VISION RESEARCH

A NATIONAL PLAN: 1978-1982

THE 1977 REPORT OF THE
NATIONAL ADVISORY EYE COUNCIL

Volume Two

Panel Reports

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service, National Institutes of Health

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Introduction

THIS VOLUME COMPRISES the reports of six Panels established by the National Advisory Eye Council to review the status and prospects of vision research and research training and to make recommendations concerning the future development of the National Eye Institute's program.

Panel Reports

These reports generally follow a common format. Each, except for *Vision Research Training*, has a foreword that gives an overview of the program and describes how the Panel undertook the preparation of its report. This is followed by an introduction to the diseases encompassed by the program, including data on their social and economic importance and a summary of recent advances that have been made in their prevention, diagnosis, and treatment. A statement of program goals and a summary of the Panel's recommendations concerning research priorities concludes the prefatory portion.

The body of each disease Panel report is a detailed analysis of the current status of research in each of several subprograms and of the requirements for continued research progress. In each subprogram, the importance of the problem is discussed, recent accomplishments reviewed, and research objectives stated. This is followed by a detailed assessment of current research approaches to the problem, from which a few are selected as the Panel's recommendations for priority emphasis. These priorities are based upon considerations of both need and opportunity. In selecting them, the Panels have taken into account the public health and scientific importance of a particular problem, reviewed the extent and nature of relevant research support by the National Eye Institute and other public and private agencies (see Volume Three of this report, *Support for Vision Research*), and judged that additional funding and research effort will likely lead to significant progress toward the solution of the problem in a relatively short time.

After deciding upon these priorities, the Panels did not attempt to rank them further; they are considered of equal importance. Accordingly, the lists of priorities that appear at the end of each chapter have not been numbered. The combined summary list of Panel recommendations at the beginning of each report is numbered for convenience, but again, there is no intent to rank priorities within or among subprograms or programs.

The report on *Vision Research Training* begins with a general discussion of government support for biomedical research manpower development. This is followed by a detailed account of the history and status of the National Eye Institute's research training programs. Each type of NEI training award is

discussed, and factors likely to affect the future of vision research training programs are examined. The Panel concludes its report with recommendations concerning the National Eye Institute's future support of research training, realistically taking into account prevailing national policies to which the NEI's program must conform.

The Panel reports differ from one another somewhat in organization, style, and approach. This is the result of innate differences in the nature of the various diseases and areas of research considered and of the latitude given each Panel chairman to develop a report format best suited both to the subject and to the expression of his Panel's views. The Council desired some uniformity in the organization of these reports but did not insist upon rigid adherence to an inflexible outline that would restrict the free flow of ideas or interfere with the presentation of special topics or concerns that any Panel wished to emphasize. (For further discussion of the National Advisory Eye Council's program planning process, see Volume One, Chapter 3.)

Project and Resource Tables

A series of tables is presented at the end of each report which provides a convenient format for presenting the Panel's recommendations in terms of numbers of recommended additional projects for FY 1978 and for displaying the financial and manpower resources that will be required to carry these projects out. (For the Council's total five-year budget projections beyond FY 1978 for each program, see Volume One, Chapter 1.)

In each report, Table 1 presents the Panel's total proposed FY 1978 budget by type of support: research grants, specialized clinical research centers, research contracts, core centers, research career awards, and research training awards. Table 2 breaks down by subprogram the number of research grants, specialized clinical research centers, and research contracts. No attempt is made to allocate core centers, research career awards, and research training awards among subprograms because these awards may encompass activities in two or more subprograms.

The estimated additional total costs for FY 1978 in each subprogram were determined by multiplying the number of recommended projects by an estimated unit cost for each type of support. This estimate is based on the average cost of such projects funded during FY 1976 and FY 1977 plus an allowance for inflation. The average cost used for research grants is $69,000; for specialized clinical research centers, from $200,000 to $400,000; and for research contracts, $100,000. Research training award estimates range from an average $15,000 for individual fellowships to $72,000 for institutional awards.

Even where the Panels do not recommend an increase in the number of projects from FY 1977 to FY 1978, they do specify additional funding to cover inflationary and other expected additional costs.

In Table 3, projects are allocated within each subprogram according to the Panel's recommendations. The numbers of projects intended as research grants, specialized clinical research centers, and research contracts are specified. For the centers, groups of related individual projects are clustered. The number of individual projects intended for each center may vary, and the increased cost of supporting centers which encompass many projects was taken into account in preparing the budget estimates.

The *Retinal and Choroidal Diseases* Panel, in the tables accompanying its report, emphasizes the relationship between basic research on the visual system and applied research on specific clinical problems. A system is used in which projects

counted in one subprogram are listed again in a related subprogram, but not counted twice. In each instance, the number of projects noted—but not counted—is enclosed in brackets, and reference is given to the related subprogram(s) in which they are counted. A similar system is used in the *Cataract* report to link projects listed in more than one subprogram to form specialized clinical research centers.

At the end of each subprogram listing in Table 3, the Panels provide estimates of the number of additional principal investigators that will be required to undertake the recommended projects during the three-year period 1978-1980. It is important to stress that the Panels do not intend these estimates to represent only newly trained investigators. The majority of these new principal investigators are expected to come from the ranks of experienced scientists, including those already engaged in vision research as well as those in other disciplines who may be attracted to working on problems involving the visual system. For estimates of the need for additional newly trained investigators in each program, see Chapter 4 of the *Vision Research Training* Panel report.

It is quite apparent from these tables that the Panels believe that the primary instrument for carrying out the goals and objectives of the National Eye Institute should continue to be the individual research project grant. It is through support provided by this mechanism, which has proven well-suited to encouraging both scientific creativity and public accountability, that great accomplishments have been made in the past. It is by the use of the investigator-initiated research grants that most of the recommendations presented in this volume will best be carried out. For further discussion of the Council's views on the implementation of these recommendations, see Volume One, Chapters 2 and 7.

A. EDWARD MAUMENEE, M.D.
Chairman
Program Planning Subcommittee
National Advisory Eye Council

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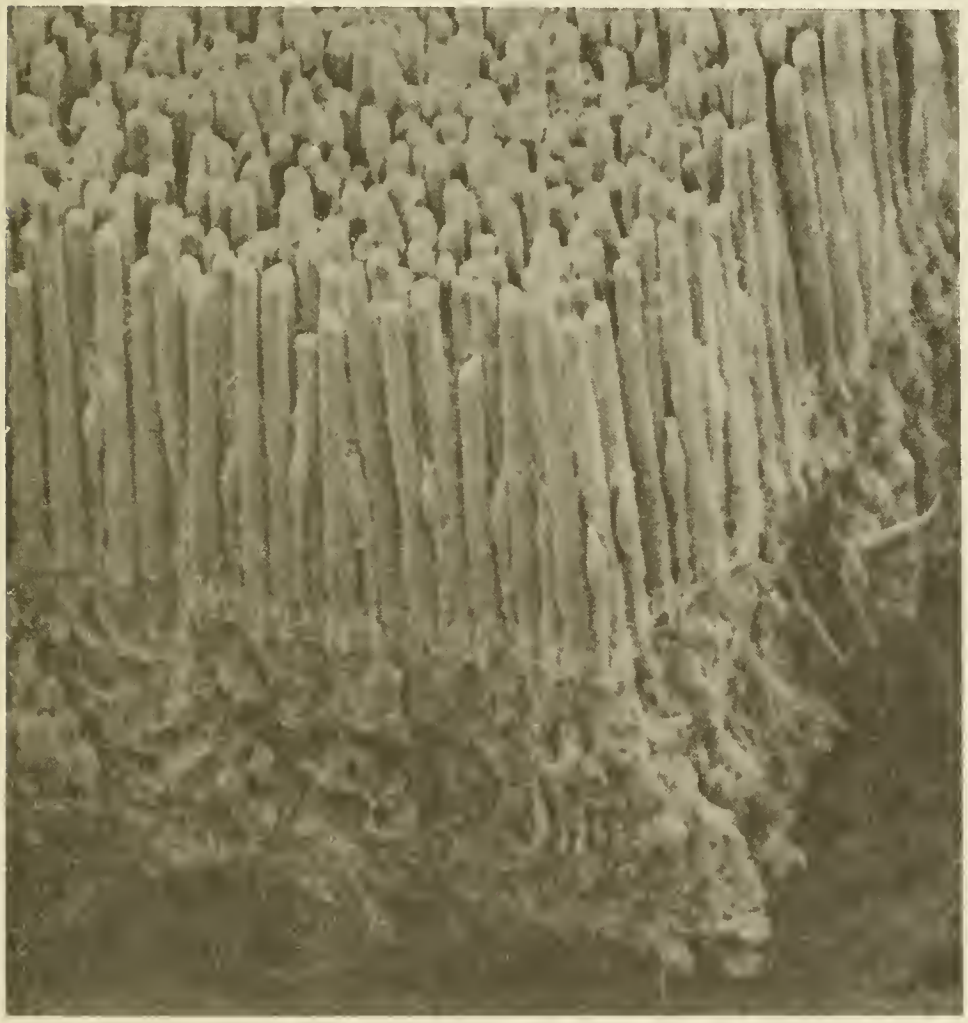
Retinal and Choroidal Diseases



Overleaf: *Scanning electron micrograph of rod and cone photoreceptor cells of the frog retina (x915).*

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Foreword

THE RETINAL AND CHOROIDAL DISEASES Panel, composed of scientists active in the field, was asked to review the National Eye Institute's research program in retinal and choroidal diseases and to report back to the National Advisory Eye Council. This document is the Panel's report to the Council on its deliberations.

This report follows and enlarges upon the *Retinal and Choroidal Diseases* section of the 1975 report of the National Advisory Eye Council. In so doing, the Panel has found it necessary to modify the subprogram categories in *Retinal and Choroidal Diseases* to expand the number of research approaches recommended in that report. As the extensive list of consultants suggests, the Panel has sought participation and advice from a broad sample of basic and clinical scientists. Using all information available to it, the Panel has outlined reasonable research goals and objectives, defining, in addition, special research needs for the future. Further, the Panel has made recommendations, both specific and general, for appropriate ways in which to accomplish these objectives and meet these needs, including a list of the manpower and fiscal resources required.

Introduction

THE RETINA, the sensory membrane of the eye, is the immediate instrument of vision. It receives visual images transmitted through the cornea, lens, and vitreous humor and converts them to electrical impulses sent to the brain via the optic nerve (see Figure 1). Damage to the retina leads to loss of vision and, when severe, to blindness.

Unfortunately, the retina is vulnerable in a remarkable variety of ways: it requires a steady supply of oxygen and nutrients for which it depends on each of two separate blood supplies; stoppage of either source of supply leads to death of the retina. Further, the retina is delicate; to live it must have a carefully controlled environment, any derangement of which can lead to loss of the retinal function on which good sight depends. The actual visual receptors, the rods and cones, serve as one example: they constantly renew essential elements of their structure; and in order to do so, the rods and cones must live in a cooperative association with a second cell, the pigment epithelial cell. Failure of either cell to perform its shared function leads to malfunction of both, evident to the affected person as loss of vision.

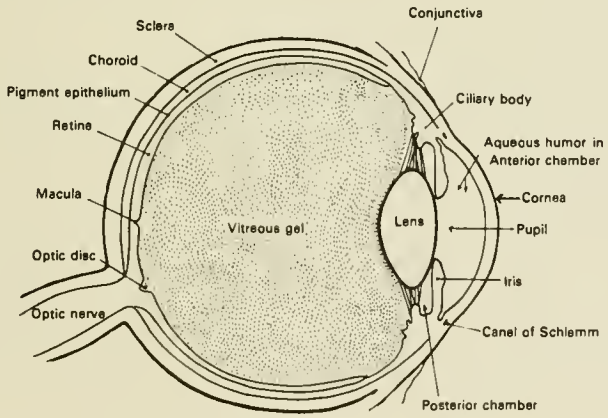

Figure 1. Cross section of the human eye.

If diseases involving the retina are diverse in origin, the research program to attack them is necessarily complex, comprising a total of 12 subprograms, ranging from hereditary problems to diseases associated with infections and from damage by toxic agents to visual problems arising from circulatory failure.

Importance

Over 1,800,000 Americans have trouble seeing even with glasses because of retinal and choroidal diseases.[1] Within this group there are 514,000 people whose vision is severely impaired. Of these, an estimated 170,000 are legally blind, making retinal and choroidal diseases as a group the leading cause of blindness in the United States. Each year, an additional 15,000 Americans become blind from these disorders.

As a primary cause of visual impairment and disability, retinal and choroidal diseases interfere with communication, seriously restrict employment opportunities, and limit mobility for a large segment of the United States population.

In 1972, the latest year in which there are adequate estimates of the economic impact of visual disorders in the United States, retinal and choroidal diseases are estimated to have cost Americans more than $1.5 billion in direct health care expenses and an additional one-half billion dollars in lost earnings. Unfortunately, neither means of cure nor prevention exists for most diseases of the retina and choroid. Lack of sufficient understanding of the fundamental processes of retinal function is the primary obstacle to further progress. Even diagnosis of these diseases may be difficult because of the relative inaccessability of the retina and choroid and because of the similar appearance of many retinal and choroidal diseases.

- *Developmental and hereditary disorders* of the retina and choroid are responsible for 20 percent of all blindness due to retinal and choroidal diseases. Most of these diseases afflict the newborn, causing them a lifetime of struggle and for their families substantial financial and emotional hardships.
- Seventeen percent of all newly recorded cases of blindness are due to *retinal circulatory abnormalities,* most of which are associated with diabetes mellitus. Other blinding disorders of retinal blood vessels include hypertension and arteriosclerosis, vascular occlusions, cystoid macular degeneration, sickle cell disease, and retrolental fibroplasia. An estimated 19,000 Americans are afflicted with severe visual impairment as a result of retrolental fibroplasia, and a study of blind school children showed that 24 percent had lost their sight from this disease.[2]
- *Myopia,* the most common eye condition, affects about 70 million Americans. Although most of these cases are simple myopia, which can be corrected by the use of eyeglasses at a cost estimated to be $1.2 billion every year, about 715,000 Americans suffer from myopia that cannot be adequately corrected; of these, 36,000 have severe noncorrectable visual impairment.
- *Tumors* of the retina and choroid, although not a frequent problem, are important because they can cause death as well as blindness. About 60 percent of those afflicted with ocular melanomas die within five years.
- Because diseases of the *macula* affect the central area of the retina responsible for high visual acuity, these diseases lead to severe loss of vision. An

[1]Except where specifically referenced, incidence, prevalence, and cost statistics quoted in this report can be found in or have been derived from: Westat, Inc, *Summary and Critique of Available Data on the Prevalence and Economic and Social Costs of Visual Disorders and Disabilities,* Rockville, Maryland, 16 February 1976. These data were derived from various sources, and care should be used in interpreting them, particularly in comparing one figure with another. Methods of data collection, age specificity, definitions of impairment, and other characteristics of the data may vary.

estimated 165,000 Americans, mainly in older age groups, develop macular disease each year. In most cases the ability to read normal sized print or to see small objects is lost.

- *Retinal detachment*, a separation of the neural retina and the underlying pigment epithelium, is diagnosed some 25,000 times a year. Although, of those cases that are due to retinal breaks, approximately 70 percent are successfully reattached with partial restoration of vision, other types of retinal detachment repair have a considerably lower success rate.

- *Inflammatory disorders* of the retina and choroid are characterized by the accumulation of inflammatory cells and fluid within tissues. These diseases commonly affect the vitreous body and the front of the uveal tract, the ciliary body, and iris. When the iris and ciliary body are affected, secondary glaucoma and cataract often result. In 1972, approximately 67,000 Americans suffered severe visual impairment from uveitis; a total of 23,000 of these were so severely affected that they were legally blind.

- Numerous ocular diseases result primarily from malfunction within the *uveal tract*. These include circulatory disorders, inflammations, and macular degeneration. The posterior part of the uveal tract, the choroid, is especially vulnerable to changes associated with aging. Some sclerosis in choroidal vessels is observed in half the population over age 60.

- The *vitreous humor*, which occupies about 80 percent of the volume of the eye, assumes considerable importance in a great number of ocular disorders. Diabetes mellitus, intraocular infection, and uveitis reach their full potential for harm as a result of changes in the vitreous body. The vitreous humor plays a major role in the common types of retinal detachment, especially those produced by foreign bodies and inflammations.

- The *visual cells* (photoreceptors) and the *pigment epithelium* are directly involved in many blinding diseases. These diseases include a number of developmental and degenerative disorders from genetic causes (including retinitis pigmentosa), retinal detachment, circulatory deficiencies, plus disorders induced by drugs, blood-borne abnormalities, and nutritional deficiencies.

- An understanding of *retinal organization* is requisite to a true understanding of vision. Because the retina is also part of the brain, any understanding of the retina provides clues to brain mechanisms. Basic understanding of retinal organization and visual adaptation is fundamental to the prevention, diagnosis, and treatment of retinal and choroidal diseases.

- *Toxic and environmental influences* on the retina are particularly important because of the nutritional requirements of that tissue. For example, drugs or other substances in the blood, which have insignificant influences elsewhere in the body, may have severe effects upon the retina.

Further evidence of the importance of retinal and choroidal diseases to public health comes from a survey of ophthalmologists: retinal diseases were listed as the group of ocular diseases these practitioners considered most difficult to treat, most in need of basic research, and most in need of clinical research.[3] Among retinal diseases, retinal degeneration and diabetic retinopathy were the disorders most often encountered by ophthalmologists in their clinical practice.

Sixty percent of research developments considered by the ophthalmologists to be the "most significant in the past five years" were in the area of retinal disease; still, 46 percent of the respondents believed that of all areas of vision research, retinal research was the most "inadequately developed"—especially research on hereditary retinal and macular degenerations and diabetic retinopathy.

Uveitis was considered an area in which hardly any significant research had been done in the previous five years; it was considered the next most difficult disease to treat after retinal diseases.

Accomplishments

The eye as an accessible organ and as a meeting ground for various disciplines presents unusual research opportunities as well as difficult problems. Ophthalmic research is a highly fertile field in which to apply recent research advances in cell biology, biochemistry, and physics and electronics. For example, based on increased understanding of the effects of diabetes mellitus on the eye and on recent advances in the production and control of powerful beams of light, a helpful treatment has been designed to control bleeding in the retina. By the use of light beams brought to point focus on the retina, it is possible to destroy abnormal blood vessels by photocoagulating them and thus lessen the risk of massive hemorrhage inside the eye with ensuing blindness.

The adaptation of other techniques from physics and electronics promises to be important in the diagnosis, treatment, and prevention of visual disorders. Parallel opportunities are found in cell biology. Exciting advances are being made toward understanding the structure of the photoreceptors which receive and transmit the visual stimulus. In turn, this new knowledge gives strong impetus to finding new means to lessen impairment of visual function.

For instance, the single observation derived from studies of protein synthesis that the outer part of the rod photoreceptor cell is renewed at its base and cast off at its tip has suggested a number of fruitful studies directed toward finding the causes of retinitis pigmentosa and of macular degeneration.

Further, new insight into diseases of the retina and the choroid may help to advance other fields of biomedical research. It can be expected, for example, that research on ocular tumors may produce findings that will be important to general oncology. In this regard, the eye offers unparalleled opportunities for observing the behavior of a tumor. What can be seen can be measured; a great deal can therefore be learned from the response to chemotherapy of tumors metastatic to the eye from the breast and other sources. Similarly, findings from study of the manifestations of vascular and circulatory diseases in the retina are clearly applicable to the state of blood vessels elsewhere in the body, just as research on inflammatory disorders in the eye provides insight into the body's general immunologic processes.

Goals of Retinal and Choroidal Diseases Research

Recognizing the opportunities that lie ahead and the magnitude of the disease problems to be faced, the Panel has set the following broad program goals to guide research in this area:

- Enhance understanding of fundamental processes underlying good vision and of their derangement in diseases of retina and choroid
- Improve the means to diagnose diseases of retina and choroid
- Discover ways to prevent retinal and choroidal diseases or to treat these diseases effectively once they occur

The National Eye Institute's research program in *Retinal and Choroidal Diseases* encompasses specific clinical disorders as well as basic research on the development, structure, and function of the eye as related to disease. The opportunity to diagnose, treat, and ultimately prevent disease depends directly upon fundamental research. Often disorders seen in the clinic help to focus research on abnormal processes, but without a full basic understanding of what the normal is, it is virtually impossible to comprehend what is wrong in the abnormal or to set to work to find the means to put it right. In order to gain best advantage toward the goals set forth above, the Panel strongly urges that adequate support be given in a sustained, coordinated fashion both to basic and clinical research studies.

In its deliberations, the Panel distinguished between research on problem areas and specific disorders and research on development, structure, and function as related to disease. The Panel also calls attention to special areas for future emphasis. The subprograms examined by the Panel are:

Problem Areas and Specific Disorders

1. Developmental and Hereditary Disorders
2. Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities
3. Myopia
4. Tumors
5. Macular Diseases
6. Retinal Detachment
7. Inflammatory Disorders

Development, Structure, and Function as Related to Disease

8. Uveal Tract
9. Vitreous Humor
10. Visual Cells and Pigment Epithelium
11. Retinal Organization and Visual Adaptation
12. Special Areas of Future Interest
    - Toxic and Environmental Disorders
    - Low Vision
    - Retinal Regeneration and Transplantation
    - Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models

In separate chapters of this report each of these subprograms is described in terms of the magnitude of the problem, research accomplishments, current research objectives, and research needs and approaches. Specific recommendations to guide research are made for each subprogram, and the resource requirements to meet these recommendations are projected.

In considering each of these programs, it must be kept in mind that the eye is one: our categories and classifications are an attempt to fit quite complicated conditions into simple molds. Some conditions fit such molds quite easily; others

do not. The problems raised by individual conditions are often interrelated, and hence, research areas are interdependent. One problem area often merges imperceptibly into others. For example, in the young eye glaucoma is often first announced by myopia—an eye under increased internal pressure grows larger, the focus of light rays shifts forward of the retina, and the individual becomes nearsighted. The same example—glaucoma—is also apt for the later years. Then a steady level of increased intraocular pressure can lead to loss of sight by impairing the circulation of blood to the optic nerve. In both examples the base condition that raised intraocular pressure could be the same; however, the precise ocular manifestation differs with age. Most important, a fault in one mechanism of the eye—for example, the control of intraocular pressure—may express itself in damage to another part of the eye.

Thus, our classification of retinal and choroidal disorders and research areas is essentially pragmatic; in the main, it lists the chief clinical problems with which we contend and enumerates individual ocular regions and disciplines. Overall, this classification reflects what has proved to be the best approach to the solution of clinical problems: to apply what is currently known in an attempt to lessen the ravages of disease while pursuing, through the intelligent development and application of basic science, means of prevention and methods of cure.

Such a two-pronged method of attack is evident in our classification. Under Problem Areas and Specific Disorders, immediate clinical problems are listed, whereas Development, Structure, and Function as Related to Disease largely relates to efforts to further knowledge of the nature of the eye and of its derangements in order to permit diagnosis, prevention, or cure of specific conditions.

Summary of Recommendations

THE PANEL'S SPECIFIC recommendations for each subprogram are provided in the respective chapters. In summary, the Panel recommends that:

1. Fundamental research studies be vigorously pursued in the following areas:
   - The specific anatomy, biochemistry, and physiology of the visual cells and pigment epithelium.
   - The characteristics of the normal retinal and choroidal circulation and of the etiology and pathogenesis of the changes which occur in diabetes mellitus and other retinal vascular diseases.
   - Macular degeneration—especially its relationship to age-related changes in Bruch's membrane, to the formation of abnormal new blood vessels, and to the metabolism of the pigment epithelium-photoreceptor complex.
   - The neurophysiology of retinal organization and visual adaptation.
   - The nature of retinal detachment.
   - Application of basic research techniques in psychophysics, electrophysiology, and fundus reflectometry to the diagnosis and understanding of clinical disease.
2. Special attention be given to the following neglected areas of research:
   - Normal and disease processes of the uveal tract.
   - The composition, structure, and pathology of the vitreous humor.
   - Normal and pathological processes in developmental and hereditary disorders.
   - Myopia—its development and its possible control. This should include an intensive study of the normal process of eye growth.
   - The nature and origin of ocular neoplasms.
   - Toxic and environmental disorders.
   - Low vision, especially improved or new ways to aid such patients.
   - Retinal regeneration and transplantation.

3. An intensive effort be made to obtain and develop appropriate animal models. Research in developmental and hereditary disorders, in macular degeneration, in retinal detachment, and in myopia is truly hampered by the paucity of such models. The value of finding and properly distributing such animals cannot be overemphasized. In the search for animal models and for animal parallels to human ocular pathology, we recognize the need to train a cadre of veterinary ophthalmologists.

4. Research be conducted to develop means for safe retinal and choroidal biopsy. Many research and clinical problems would greatly benefit were such techniques available. Retinal tissue is especially needed for research on uveitis, on developmental and hereditary disorders, and on inflammatory disorders. A safe biopsy technique should first be developed in lower animals and then perfected in primates. The National Eye Institute should consider establishing a special support mechanism to encourage work in this area.

5. The National Eye Institute should also seek to develop a national registry for correlative ophthalmic pathology in cooperation with local eye banks. The sense of this is clear. There is an urgent need to collect, preserve, and distribute eyes. There remains an unfilled need for accurate, intensive, correlative clinical histopathologic studies. This would entail the establishment of a roster of patients who have been adequately examined and followed longitudinally and who have agreed to will their eyes to the eye pathology bank. This would be of special importance to the study of macular degeneration, retinal detachment, hereditary retinal degeneration, and a host of other visual disorders. If biopsy specimens become available, they could also be included in the registry.

   However, if the full promise of such an endeavor is to be realized, there is a further need that must be met: it is imperative that such studies be of a broader scope than is the current, common practice; specifically, that pathology move beyond its present confines to include biochemical and immunological research. In short, pathology should attempt to lead the way to an understanding of cause. (For further detail, see page 109.)

6. The toxic effects of drugs, chemicals, and environmental pollutants on the retina and choroid be studied.

7. Diagnostic techniques be devised for inflammatory disorders in the absence of direct biopsy.

8. Comparative clinical data be collected and evaluated with regard to the use of vitrectomy.

9. The National Eye Institute should establish a mechanism for interagency coordination of vision research, particularly research on retinal and choroidal diseases. This is especially important for toxic and environmental hazards.

10. Provision be made for continued evaluation of the research program in retinal and choroidal diseases. A formal evaluation, such as this Panel has done, should take place periodically, at least once every five years. Evaluations should be designed to review the ongoing program in terms of program objectives, to delineate accomplishments, and to redefine priorities in terms of the research needs at a given time.

Summary of Resource Requirements

IN FISCAL YEAR 1977 the National Eye Institute will devote approximately 40 percent of its budget, or an estimated $23,125,000, to the research program in *Retinal and Choroidal Diseases.* These monies will support 264 individual research grants, two specialized clinical research centers, 53 research contracts, and other research work in this area in accordance with the priorities outlined in the previous report of the National Advisory Eye Council.

The Panel has recommended a considerably expanded program in retinal and choroidal diseases. We have recommended support of new areas, pointed out areas of neglect, and set forth additional research needs and approaches in already established areas. Current resources are inadequate to meet these needs. To provide for necessary expansion, we recommend that the total level of support for research in retinal and choroidal diseases be increased to approximately $27 million in FY 1978 and thereafter increased moderately for each of the next five years. These monies will be required to support the recommended research projects.

This expanded program will require additional specialized manpower. The Panel recommends in this regard that:

- An additional 208 principal investigators be supported in retinal and choroidal diseases research.
- Consideration be given to attracting people from other specialties to vision research, e.g. veterinary medicine and immunology.
- Further, specialized retraining opportunities be made available to researchers already working in vision. An active and continuing effort must be conducted within the eye research community to make the most productive use of the skills and talents already present.
- Stability of support be ensured for established researchers.
- Active recruitment of young investigators interested in eye research be initiated. A mechanism must be fashioned to provide them with appropriate training.
- Training both in clinical and basic aspects of vision research be promoted.

1

Developmental and Hereditary Disorders

DEVELOPMENTAL AND HEREDITARY disorders afflict newborn and young children and therefore instill fear in many prospective parents, especially those with known family tendencies toward these diseases. Unfortunately, such disorders are relatively common; at present, they are responsible for an estimated 33 percent of all blindness among school children in the United States.[2] In retinitis pigmentosa, one of the more common hereditary retinal degenerations, a huge, ring-like area of blindness slowly encroaches on a central island of vision. See Figure 2.

The impact of a visual disability evident from birth is immense. There is the immediate emotional impact on the family and the long-range effect of trying to cope with a blind child growing up in a world arranged for the sighted. In addition, there are special costs to the family and to society. Most important, there is a long and difficult struggle for the blind child who tries to gain an education and

Figure 2. Simulated vision in one stage of retinitis pigmentosa.

prepare for a useful career, all the time knowing that his or her performance must approach that of sighted people if opportunities are to be won.

Things are not much easier for those born with the devastating conditions which destroy vision in young life. For these children, the teens are a bitter period in which, as their vision is gradually lost, they must surrender cherished daily pleasures in school and sport, preparing themselves instead for an adulthood of blindness.

Accomplishments

A significant research effort in developmental and hereditary diseases has come into being during the past several years. Although little can be done at present to prevent the onset and progression of these diseases, important research advances have been made. To date, the combined efforts of the anatomist, geneticist, physiologist, biochemist, and clinician have served to clarify several aspects of these disorders. Some of these accomplishments are in:

- *Diagnosis.* Certain inborn errors of metabolism can be diagnosed by blood studies. For example, in the systemic disorder known as Tay-Sach's disease, a deficiency of hexosaminidase A is found in the blood of affected children.[4] Of great importance in a disorder of the choroid and retina called gyrate atrophy is the recent finding of an elevated level of the amino acid ornithine in the plasma. This represents the first indication of a specific biochemical defect in individuals with this rare but blinding retinal degeneration.[5] As evidence of the potential of a discovery of a biochemical marker in conditions of this type, the original finding of elevated levels of plasma ornithine has rapidly led to a series of advances in the understanding of this disorder. An intensive search for a specific biochemical defect has now produced strong indications that a single enzyme, ornithine ketoacid transaminase, is at fault.[6-8] On this basis, rational attempts at treatment have already begun.[7]

- *Identification of the genetic carrier.* Of equal importance, once the specific biochemical defect responsible for an inborn error of metabolism is discovered, the way is clear for the identification of carriers of the recessive gene. Even though normal in appearance, carriers may be detected through careful biochemical assays; they have a partial defect.[4,9] Thus, a biochemical test performed on a sample of urine, blood, or tears provides a sensitive and harmless way of locating an uninvolved bearer of the gene as well as diagnosing those actually afflicted with the disorder. Such measurements form the groundwork for rational family planning.

- *Therapy.* As a direct result of the discovery of specific biochemical defects in several disorders, rational attempts at therapy can now be attempted. Indeed, in a condition called abetalipoproteinemia, an effective treatment has been found.[10]

- *Chromosomal abnormalities.* Quite distinct, but equally important, specific chromosomal abnormalities or faults have been noted both in a developmental disorder, retinal dysplasia, and in the life-threatening ocular tumor, retinoblastoma.[11]

The ultimate goal of these studies is to prevent the occurrence of these disorders or, failing this, to treat effectively those in whom it occurs. Success in such endeavors depends not on a single study but, most often, on a combination of efforts. Such efforts have led to the prevention of the generalized retinal

degeneration associated with the disease abetalipoproteinemia referred to above.[10] This disease, in which there is a spectrum of findings—including spiny erythrocytes, celiac disease, diffuse neuromuscular disease, and generalized retinal degeneration, is caused by an abnormality in one of the groups of lipid transporting proteins, the beta-lipoproteins. Consequently, fat absorption from the intestine is defective, and the blood is low in certain fats including the fat-soluble vitamins. Since one of the fat-soluble vitamins, vitamin A, is needed to maintain the rods and cones, deficiency leads to the death of these cells and hence to blindness. By the use of intramuscular injections of vitamin A, patients with a-betalipoproteinemia show remarkable improvement; they increase their dark-adapted sensitivity, and in one treated patient, the electrical responses of the eye returned to normal. From all indications, a good long-term result is also to be expected. These results are encouraging for this is the first instance in which retinal function in a patient with a generalized retinal degeneration has been improved by treatment.

Vitamin A can be mentioned again as an illustration of the rapid progress in biochemistry of the retina. There has been a splendid series of studies in which the sequential and specific characteristics of vitamin A transport to the eye have been defined, opening up new vistas for investigation in clinical disorders.[12,13]

Although major emphasis has been placed on biochemical advances, other approaches are also being pursued. Thus, the interrelationship of virus infection to genetic expression has been highlighted by recent studies implicating virus infection and resultant chromosomal abnormalities in producing retinal dysplasia.[14] Likewise, advances in electrophysiologic and psychophysical testing; progress in the development of animal models; and, finally, an improved understanding of the functioning of the normal retina and choroid are each evidence of a broad-based effort.

Research Objectives

- Develop techniques for the prenatal diagnosis of developmental and hereditary disorders
- Identify carriers of genetic traits which lead to blinding retinal disorders so that appropriate genetic counseling may be offered
- Discover the specific cause of each hereditary retinal disorder so that a rational treatment can be found to reverse or to halt its course
- Develop nonhuman models of these diseases
- Undertake carefully designed clinical trials when promising therapeutic measures become available

Research Needs and Approaches

The major research approaches in this area during the next several years must build upon present knowledge, must be designed to gain new knowledge, and must bring to bear technical capabilities, all in an effort to help resolve a baffling array of difficult clinical problems. Future accomplishments will depend on understanding the normal retina and finding the causes of hereditary retinal degenerations.

The Normal Retina

Our understanding of the normal retina must be improved, for it is impossible to study and understand the abnormal without reasonable knowledge of the normal: the two are constantly compared. And, in attempting to explain the generalized degenerations of the retina, the close relationship between the retinal pigment epithelium and the photoreceptors must be considered. They act together; one is dependent upon the other. This is not surprising since all of the elements upon which the life of the neural retina depends (proteins, carbohydrates, etc.) pass across the pigment epithelium to nourish the cells of the outer retinal layers. In addition, many of the vital processes of human vision involve exchanges of substances (vitamin A) and movement of waste products (extruded rod outer segment discs) between these tissues. Although precise knowledge of the mechanisms involved in these processes is just now being gained, it is likely that a disturbance in such mechanisms constitutes the basic disease process in the inherited retinal degenerations.

- *Interrelationships among retinal cells.* The complex interrelationships among retinal cells are not precisely understood. Correlations of cellular organization with the electrical discharges of the retina and their relationship with transmitter substances remain unresolved. In fact, there is incomplete knowledge of the identity and role of chemical neurotransmitters in the retina. The opportunity to modify, isolate, or eliminate experimentally selected responses in the eyes of laboratory animals, vertebrate or invertebrate, is of primary importance to an understanding of retinal function in man.

  In this regard a number of recently developed technical advances have made it possible to explore the microstructure and function of interrelated cells. For instance, it is now possible to record an electrical signal from a single cell and then to inject into it a dye for later anatomical identification thereby affording new insights into normal function.[15]

Through the intelligent application of available investigative techniques, greater information is urgently needed about:

- *Membrane architecture* in normal and degenerating cells. Specific information is lacking about the structure and relationships of retinal cells that could provide clues to the primary site in a disease process. Involved here are ultrastructural studies using freeze-fracture techniques as well as high-resolution transmission and scanning electron microscopy.

- The *physical properties of the cellular membranes* across which all communication among cells occurs. The interactions of the pigment epithelium, photoreceptors, neural cells, and glial tissues are all important to clarify the nutritional, chemical, and electrical exchanges through their various cell membranes.

- *Metabolic processes and active transport* between cells of the pigment epithelium, photoreceptors, Müeller's cells, and blood vessels. These should be examined biochemically and electrophysiologically. Normal processes should be defined and the extent to which they have been compromised in developmental and hereditary disorders needs to be determined.

- *Tissue culture of the pigment epithelium.* Although precise details are yet to be uncovered, it is now thought that this cell layer is involved in many of the hereditary diseases of the retina.[16] Improved laboratory technology has made it possible to maintain cultured pigment epithelial cells in good condition for long periods of time.[17] Since the primary site of involvement in

many of the generalized retinal degenerations lies in the pigment epithelium/photoreceptor complex, comparative studies of normal and abnormal pigment epithelial cells could well provide the morphologic and biochemical clues needed to solve the riddle of these diseases. Tissue culture techniques permit experimental manipulations not otherwise possible.

Development of Hereditary Retinal Degenerations

Research in Humans

Clearly, if these progressive disorders are to be understood, it is first necessary to establish the precise locus of the disease process. This can be pursued in several ways. Over the past ten years, there has been a marked improvement in our ability to interpret the electrical responses of the human eye through use of electroretinography (ERG).

The use of the electroretinographic latency measurements in clinical recordings has proved important to the clinical understanding of hereditary retinal degenerations, for such measurements have led both to a better classification of the various forms of these diseases and to an improved capability for distinguishing progressive degenerations from other retinal diseases which may look ophthalmoscopically similar.[18] In like fashion, use of the early receptor potential (ERP) has helped in the classification of these disorders.

For electrical recording, the development of *focal stimulation* of the eye should be encouraged. As a diagnostic tool, this would be especially applicable to macular disease. In the study of generalized degenerations of the retina, such tests would be helpful in the study of ophthalmoscopically normal retinal areas. In many of these diseases, the degree of degeneration throughout the retina and choroid varies markedly. This is particularly true in certain of the hereditary peripapillary degenerations and of the degenerations which begin peripherally and move centrally. One present drawback of the standard ERG and electro-oculographic (EOG) recording is that they are mass responses, dealing with the totality of retinal receptors.

A powerful tool yet to be fully exploited is *fundus reflectometry*, whereby the kinetics and amounts of the visual pigments of the intact human eye can be studied in harmless fashion, thus permitting a direct evaluation of visual function. Such a test has been important in finding that the basic abnormality in fundus albipunctatus is a retarded regeneration of the visual pigments.[19] It has also been helpful in determining that in the rod monochromat the only pigment available in the retina is the rod pigment, rhodopsin. This supports those histologic reports which claimed a near-absence of cone receptors.[20] So far, only a few attempts to use this technique in conjunction with other tests of retinal function in the generalized retinal degenerations have been made. In the future, this test could help answer questions such as: What are the concentrations and kinetics of visual pigments in human eyes during the development of a retinal disease? Is an overgrowth of photoreceptor outer segments characteristic of human retinitis pigmentosa? Are the enzymatic processes by which visual pigment is synthesized affected? What is the relationship between changes in visual pigment and the loss of vision in different retinal regions?

Animal Models

Since developmental and hereditary diseases of the choroid and retina are rarely life-threatening, and usually are not thought of at death, it has been

virtually impossible to obtain eyes for histologic and biochemical study. In the absence of such material, research progress has been slow. One avenue that is just beginning to be explored with success is that of animal diseases resembling human hereditary retinal degeneration.[21] Combining a thorough investigation of the human disease with the development and study of animal models offers the best chance of making significant advances. Such models become even more important as the human disease is clarified. For it is only in animals that planned biochemical and metabolic studies of retinal tissues can presently be accomplished. To this end, rodents and dogs with inherited retinal degeneration are being bred and studied and there are now several animals which bear promising resemblances to retinal degenerations in man. In the future, pathologic and electrophysiologic studies should be pursued and specific biochemical defects should be vigorously sought to account for the retinal degenerative changes.

It should be added that the existence of animals with inherited retinal degeneration presents a second opportunity. Not only can they help in the search for cause, they can also play a large role in the development of a treatment: first, to make sure that a proposed treatment is safe, and second, to help to find out if it is effective. It is far more accurate to measure the effects of a treatment when it can be tried on littermates living under the same daily regimen than it is to measure the effects in unrelated humans differing distinctly in the severity of their disease and in the way in which they live.

To accelerate these important studies, the National Eye Institute should consider establishing a facility for breeding currently unavailable animal models for distribution to investigators. Certain breeds of dogs which are particularly appropriate models of human disease are presently difficult to obtain and expensive to keep. Most investigators are therefore unable to study these excellent animal models. An annual investment of one-sixth of one percent of the NEI budget would sustain a worthwhile colony.

Specific Biochemical Abnormalities

Among the hereditary retinal degenerations in humans are several in which there are also systemic abnormalities. Even though these have been only partially explored, biochemical abnormalities have already been identified in some of them. These diseases offer an unparalleled challenge to compare the normal to the abnormal and, ultimately, through biochemical intervention, to affect favorably the course of a disease. It should be added that here, too, animal models offer a great potential: if a comparable biochemical defect is defined, prospective remedies can first be evaluated in animals.

Of course, this potential also adds impetus to the search for biochemical abnormalities in retinal degenerations unassociated with a known systemic defect. Until recently, biochemical defects were known only for multisystem disorders, but recent work has shown, as noted under Accomplishments, that in a localized retinal disease, gyrate atrophy of the choroid and retina, there also can be evidence of a systemic abnormality; in this case an elevated level of plasma ornithine.[5] While it is unlikely that the high ornithine level itself is responsible for the retinal degeneration, this finding will help direct future investigations into a search for the precise catalytic enzyme whose function is deranged.

In addition, the idea that a retinal degeneration can stem from a nutritional deficiency is supported both by early studies in vitamin A deficiency[22] and by more recent experiments which demonstrated that cats fed a taurine-deficient diet go blind.[23] It is clear that all phases of the biochemical and nutritional basis of retinal disease must be actively pursued.

Biochemical Genetics

There is now good evidence that in certain inborn errors of metabolism the unaffected carrier of a genetic disorder can be identified;[9,24] thus heterozygote detection is within the sphere of biochemical diagnosis, an area of great importance in genetic counseling. This is particularly applicable to disorders in which a systemic disease is associated with a retinal degeneration, for here a detectable biochemical defect can be anticipated. Heterozygote detection has already been accomplished through biochemical analysis in certain of the inborn errors of metabolism.[4,9] Heterozygotes have also been detected by means of the electro-oculogram in vitelliform retinal degeneration, a condition limited to the eye.[25] With newer and more sophisticated clinical tests at hand, this type of information will be more readily obtainable in the future and obviously will greatly aid in the rational genetic counseling of young couples.

Genetic Linkage Analysis and its Relevance to Hereditary Retinal Disease

In the search for help in genetic counseling, attention is rapidly turning to linkage analysis. Linkage analysis has as its ultimate goal the assignment of genes to specific chromosomes by determination of neighboring genes.[26] Success depends on the fact that there is a strict order to the genetic map and that in a sense, an otherwise invisible gene can at times be recognized by the presence of its neighbors. Determination of neighboring genes thus is essential. A knowledge of linkage associations might then permit determination of the risk to supposedly unaffected family members of a disease with a delayed onset. Indirect diagnosis based on marker loci known to be closely linked to the disease locus can also make it possible to limit these diseases, either by prenatal diagnosis and termination of pregnancy or by identification of unaffected carriers prior to their having offspring. In addition, linkage analysis may help to determine whether a specific disease is caused by allelic mutations at only one gene locus or whether there is nonallelic heterogeneity.

Other Research Areas

Several other areas of research into the pathogenetic mechanism of generalized retinal degenerations warrant continuing and active support.

First, the *effects of light on the retina* and the action of excess light on the retinas of patients with hereditary retinal degeneration should be studied. Ten years ago scientists first delineated the effect of excess light on the normal retina and its ability to produce degenerative changes in the photoreceptors after light exposure.[27] This observation was an outgrowth of the finding that rats fed a vitamin A-free diet to produce a nutritional retinal degeneration were protected by dark-rearing. The exact levels leading to light-induced degenerations, the precise pathogenesis of light toxicity, and the variability of effect on normal, diseased, and nutritionally deficient retinas deserve further study.

Second, investigators should pursue the recent finding by several groups of workers that an *antigenic reaction* involving the rod outer segments can be produced by antibodies against the proteins of the rod outer segment.[28,29] While such studies might also be applicable to the inflammatory diseases of the eye, there are provocative clinical studies suggesting the participation of immune responses in some retinal degenerations.

Third, a relationship between *chromosomal abnormalities* and some developmental diseases of the retina (retinal dysplasia and retinoblastoma) has now been demonstrated.[11] However, the etiologic factor that triggers this chromosomal

change is still unknown. In this connection, promising research has been undertaken concerning the influence of viruses on genes, but the exact nature of changes important to the retina remains to be clarified.

Priorities and Recommendations

- Continue intensive research on basic science of the retina.* Studies of the normal retina should emphasize:
  - Cellular interrelationships.
  - Cell membrane architecture.
  - Cell response relationships.
  - Metabolic processes and active transport.
- Continue and expand research to define the pathogenesis of the hereditary retinal degenerations. This research should include:
  - Development of improved clinical diagnostic techniques.
  - Active collection of eyes from affected individuals at death or surgery—especially those whose clinical condition has been previously well-documented. Only by obtaining such tissues will it be possible to study the pathogenesis of these disorders through tissue culture of diseased pigment epithelium, biochemical investigation, and ultrastructural studies.
  - An active program for the breeding and distribution of appropriate animal models. The present support for the production of RCS rats should continue. New initiatives should include a search for and the breeding of primates, dogs, and cats with hereditary retinal degenerations.
  - A search for specific biochemical abnormalities in these diseases.
  - Related research on light degeneration studies, on antigenic reactions of photoreceptors, and on the relationship between chromosomal abnormalities and retinal disease.

Resource Requirements

The requirements for meeting these recommendations in *Developmental and Hereditary Disorders* are provided in the tables at the end of this Panel report. For each recommendation, we have designated the number of additional projects required and the cost for supporting these projects on an annual basis. Estimated FY 1977 NEI funding for this subprogram will be $1,159,000 for support of approximately 16 research grants and one specialized clinical research center. Additional requirements for FY 1978 include an increase of 18 research grants and two centers. These increases will cost an estimated $2,051,000, bringing the total FY 1978 funding of this subprogram to approximately $3,210,000.

* For detailed recommendations, see Chapter 9, *Vitreous Humor*, Chapter 10, *Visual Cells and Pigment Epithelium*, and Chapter 11, *Retinal Organization and Visual Adaptation*.

2

Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities

RETINAL VASCULAR DISEASE is a leading cause of blindness in the United States. One-sixth of all newly recorded blindness in 1970 was attributed to retinal circulatory abnormalities.[30] In this regard, it should be noted that the retina is nourished from two different sources: the retinal blood vessels, which have been extensively studied, and the choroidal blood vessels, which are essential to vision but which have not been studied in any detail because of technical limitations.

Most blindness caused by retinal vascular disease is associated with diabetes mellitus.[31] Diabetic retinopathy causes permanent damage to the retina in many ways: in places, retinal blood vessels close up and blood flow stops; other blood vessels begin to leak; still others grow fragile new offshoots which break and bleed.[32] Such bleeding within the eye from newly-formed vessels can destroy all sight. Unfortunately, once the retina is hurt in this way, it cannot be repaired nor can it be replaced by transplantation.

Diabetes mellitus is not the only such threat to vision; other important diseases of retinal blood vessels which can produce blindness include hypertension and arteriosclerosis, vascular occlusions, cystoid macular degeneration, sickle cell disease, and retrolental fibroplasia. Disease of the choroidal blood vessels can be divided into two categories: those affecting large choroidal vessels, which cause extensive damage to the retina, and those which are localized to the choroidal capillaries. The latter are particularly important because they often affect the macular area, leading to macular degeneration with consequent loss of reading vision (see Chapter 5, *Macular Diseases*).

Luckily, most diabetics in the United States—approximately 10 million—will not suffer major visual loss from diabetic retinopathy. However, many will. It has been estimated that over 300,000 are threatened with blindness. Surely, this presents a vast public health problem as well as an overwhelming tragedy for each affected individual.

In any approach to the problem of retinal and choroidal vascular disease, there are three types of vascular abnormality that must be considered in detail: vascular closure, vascular leakage, and new vessel growth. As mentioned in connection with diabetic retinopathy above, diseases that impair retinal function by affecting the retinal vessels invariably do so by causing blood vessels to close off, leak, or

grow abnormal, fragile offshoots that bleed. The effort to understand, prevent, and correct each of these abnormalities forms the core of NEI's support of retinal vascular disease research.

- *Retinal blood vessel closure.* The blockage of blood flow through a retinal artery, capillary, or vein deprives the retinal neurons of oxygen, glucose, and other substances essential for life. At present, there is virtually no understanding of the pathogenesis of capillary closure. Things are somewhat clearer for larger caliber blood vessel disorders, but even here our understanding is deficient.
- *Retinal blood vessel leakage.* Protein-rich fluid leaks from damaged retinal blood vessels in a manner similar to the way in which fluid leaks in allergic reactions to produce a hive on the skin. Even small collections of fluid among the retinal nerve cells disrupt their function and produce local blindness; larger collections of fluid can lead to retinal detachment.
- *New blood vessel growth (neovascularization).* New blood vessels grow as buds from existing retinal blood vessels. However, new blood vessels are particularly leaky and fragile and threaten total blindness because of their propensity to bleed massively within the eye. Even if an eye survives massive bleeding, vision is often threatened by growing scar tissue that pulls on the retina thereby detaching it.

The specific disease entities listed below are representative of some of the conditions that produce retinal vascular closure, leakage, or new vessel formation. The complications of each disease require individual study; however, there may well be some mechanisms common to all.

Diabetic Retinopathy

It is now known from the nationwide collaborative Diabetic Retinopathy Study sponsored by the NEI that the risk of blindness from the neovascularization of diabetic retinopathy can be significantly reduced by photocoagulation. However, this treatment does not prevent diabetic changes from taking place in the eye, and there are still many patients who do not respond to this form of therapy. Additionally, diabetic retinopathy produces vessel closure and vessel leakage which is not helped by photocoagulation. Thus, despite recent advances, diabetic retinopathy continues to be a major cause of blindness.

Retrolental Fibroplasia, or Blindness of Prematurity

Now that it is recognized that an oversupply of oxygen to the premature infant is associated with retrolental fibroplasia,[33] this disease is less common; it no longer represents the largest single cause of infant blindness. Yet, hundreds of cases of retrolental fibroplasia continue to be reported in the United States each year, in part because no technique has been perfected to establish how much oxygen is actually reaching the infant eye on a minute-to-minute basis. Several considerations make it clear that blood oxygen levels of the premature infant are measurable on a continuous basis; the practical application of such diagnostic means could reduce the incidence of blindness from this cause.

Central Retinal Vein Occlusion

A blockage of the major vein draining blood from the retina can produce permanent blindness. Pilot studies have demonstrated that certain medications

might "dissolve" the thrombus, but there is still no conclusive evidence of the efficacy of these drugs.

Branch Vein Occlusion

Often, especially in association with hypertension and arteriosclerosis, a branch of the central retinal vein becomes occluded. Pilot studies have suggested that laser photocoagulation in the affected retinal region can limit the chance of bleeding from new blood vessel formation, but further carefully controlled clinical trials are required to judge whether these early indications are in fact valid.

Major Retinal Artery Occlusion

Occlusion of the central retinal artery is followed by immediate blindness. If the circulation is restored within minutes, vision can return. Recently, it has been recognized that in addition to the familiar arteriosclerotic and hypertensive changes, the central retinal artery is also subject to inflammation. The nature of this inflammation is poorly understood and urgently needs further study.

It is also now recognized that after some types of central retinal artery closure, the circulation of blood often becomes reestablished in subsequent weeks. Were there an artificial means of supplying the retina with its requirement of oxygen and nutrients during the intervening time, irretrievable visual loss could be avoided.

Sickle Cell Disease Retinopathy

Because an estimated 10 percent of the Black population in the United States carries the gene for sickle cell diseases, sickle retinopathy continues to be a very real threat to the vision of many in our population. Peripheral retinal arteriolar closure is the hallmark of sickle retinopathy; unfortunately, retinal neovascularization and hemorrhage often follow, leading to marked visual loss.

Accomplishments

Fluorescein Angiography

Over the past ten years, eye research has developed a safe and effective technique to photograph the retinal blood vessels in the living human eye. This technique, now in widespread clinical use, is so sensitive that it permits the ophthalmologist to identify a vascular abnormality as tiny as 1/100 of a millimeter in diameter.[34] Figure 3 demonstrates this technique, called fluorescein angiography, and compares the retinal blood vessels of a normal eye to those of a seriously affected diabetic eye. Blood vessels in the angiogram appear white because of a dye which has been caused to fluoresce by special photographic techniques. In the photograph of the diabetic retina, there is leakage of fluid at "A," blocked blood vessels at "B," and numerous dot-like irregular vessel abnormalities in areas such as those indicated by "C." The test is simple to perform: a harmless fluorescent dye is injected into a vein in the arm. When the dye reaches the retinal circulation, the large and small blood vessels in the retina fluoresce and stand out in sharp contrast when illuminated with blue light.

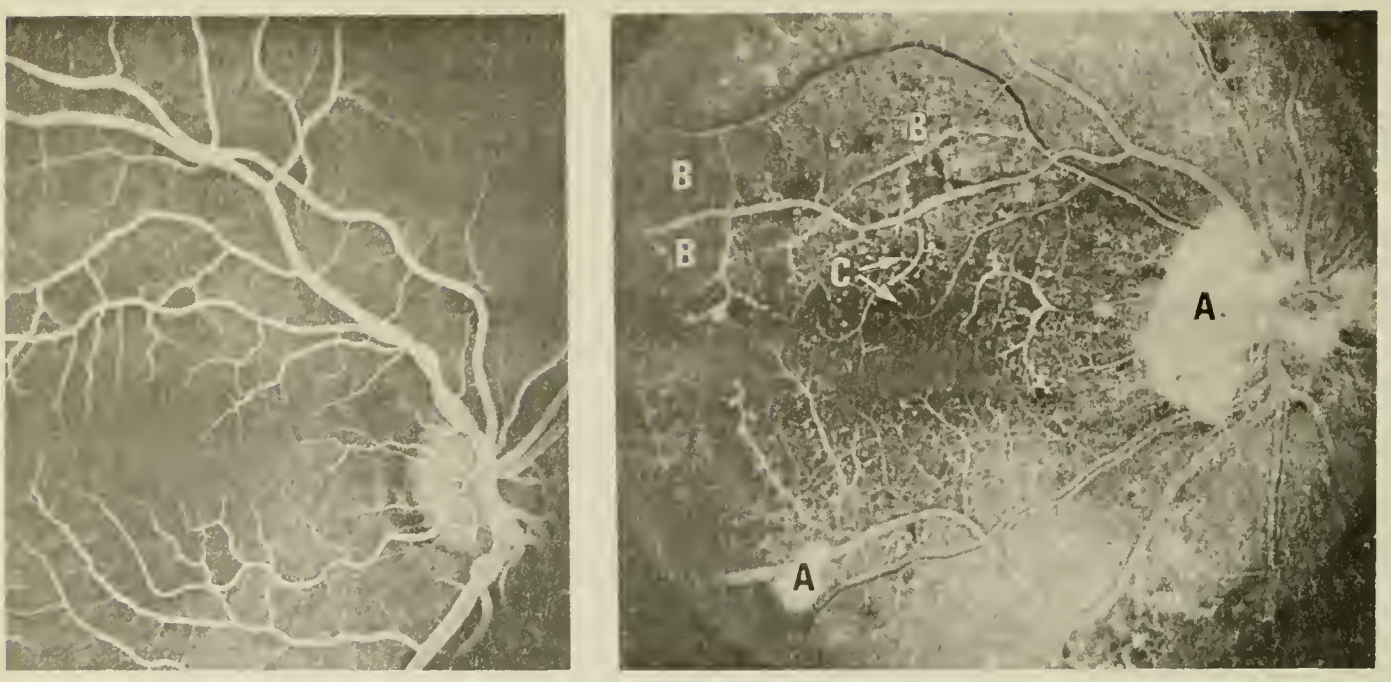

Figure 3. Fluorescein angiograms of a normal eye (left) and an eye with diabetic retinopathy.

The development of an effective and safe way to visualize the retinal circulation has given strong impetus to efforts to discover an equally effective method to visualize the choroidal circulation. Several favorable developments in this regard have already occurred; there is every chance that a clinically practical and effective method will be forthcoming.[35]

Blood Flow and Oxygen Saturation

In addition to devising means to visualize retinal blood vessels, new techniques are now in an advanced state of development which will permit an accurate evaluation both of blood flow and of oxygen saturation of the blood within individual blood vessels.[36,37] Based in large part on the measurement of the absorbance and scattering of the column of blood within single retinal blood vessels, these new techniques have implications that go far beyond the bounds of ophthalmology. For instance, the ability to measure small changes in oxygen saturation in arteries in a harmless manner may make it possible to measure precisely the response to treatment of patients with common chronic pulmonary problems such as emphysema. The technique also has implications for the management of heart failure.

The Photocoagulator: Blood Vessel Surgery

Fluorescein angiography permits ophthalmologists to recognize abnormal leakage of protein from retinal blood vessels. The development of the xenon photocoagulator and the ophthalmic laser photocoagulator offers a new approach to treating these abnormalities.[38] Once these instruments became available, the ophthalmic community rapidly recognized that the intense beam of light they

provided could be brought to a focus to seal off single, abnormal retinal blood vessels. Extensive basic investigations requiring multidiscipline efforts among scientists with knowledge of physics, anatomy, pathology, and biochemistry led to this development. Through its use, thousands have been saved from blindness.

Diabetes Mellitus: A Successful Clinical Treatment Research Program

As skill in fluorescein angiography and photocoagulation increased, it seemed apparent to a number of clinicians that xenon arc and argon laser treatment was of benefit, that it did in many instances prevent or delay blindness from diabetic retinopathy. However, clinical observation on a chance basis can be misleading. Patients with diabetic retinopathy can have spontaneous improvement of their disease without any treatment.[39] In order to establish clearly whether or not retinal photocoagulation did lessen the risk of blindness, the National Eye Institute sponsored a large, nationwide, carefully controlled clinical study to compare in a precise fashion the effects of photocoagulation treatment to the natural (untreated) course of diabetic retinopathy.

The Study, in which over 1,700 patients and 16 United States medical centers participated, clearly showed that photocoagulation treatment substantially reduces the risk of blindness from diabetic retinopathy. Data collected over a two-year period demonstrated that such treatment reduced by more than one-half the risk of blindness in moderate to severe stages of the disease. These exciting results from the Diabetic Retinopathy Study after only two years of data accumulation exemplify the type of clear answers available when a controversial clinical treatment is evaluated by properly planned clinical trials.[40]

Sickle Cell Disease, Arteriosclerosis (Branch Vein Occlusion), and Retrolental Fibroplasia (Blindness of Prematurity)

Several diseases have deleterious effects on the retinal blood vessels. In sickle retinopathy, an abnormal form of the red blood cell blocks the retinal arterioles; thereafter, new blood vessels may grow, eventually to bleed within the eye and cause blindness. The efficacy of laser photocoagulation in this disease seems to parallel that in the treatment of diabetic retinopathy.

Occlusion of a retinal vein is thought most often to be a local consequence of arteriosclerosis and hypertension. This condition is being discovered more frequently by the now widespread use of fluorescein angiography in diagnosis. Currently, there is discussion of how best to treat the proliferative vascular complications that follow the closure of a central retinal vein.

Coincident to the widespread use of oxygen to rescue premature infants, a complication of oxygen therapy—retrolental fibroplasia or blindness of prematurity—became the single largest cause of infant blindness in the early 1950's.[33] Research studies demonstrated that in susceptible newborns excess oxygen sets off a tragic series of events: first, a closure of the incompletely formed retinal blood vessels, then a subsequent growth of fragile new blood vessels that can bleed and destroy vision. With the judicious limitation of oxygen therapy in the newborn, the incidence of retrolental fibroplasia has been reduced; however, oxygen therapy remains a significant cause of infant blindness because of the difficulty in precise, continuous monitoring of blood oxygen levels and because of differences in retinal vascular sensitivity to oxygen.

Diabetic retinopathy, sickle disease, branch vein occlusion, and retrolental fibroplasia are examples of blinding retinal vascular abnormalities that are beginning to come under the ophthalmologist's control. Extensive research

efforts, as exemplified by the development of fluorescein angiography, photocoagulation,[38] and controlled clinical trials, have shown realizable benefits in preventing blindness. Past ophthalmic research in retinal vessel abnormalities clearly demonstrates the potential clinical benefit from broadly-based support of both basic and clinical investigations.

Research Objectives

The partial success to date in the fight against diabetic retinopathy is an illustration that something can be done against a major cause of visual impairment. However, much remains to be done. Diabetic retinopathy is still a frightful problem. Thus a major research objective in ophthalmic research continues to be to:

- Develop better treatment methods for diabetic retinopathy and other retinal vascular and circulatory abnormalities

There are other retinal vascular problems such as vascular occlusions for which all attempts at treatment have failed. Because of the large number of metabolic, anatomic, and physiologic mechanisms that contribute to the development of the different types of circulatory retinopathies, other major objectives in this subprogram are to:

- Gather data on normal circulation in the retina and choroid by noninvasive techniques
- Understand better the fundamental disease processes underlying these conditions
- Seek ways to prevent these diseases
- Conduct research on appropriate treatment methods

Research Needs and Approaches

There are a great many avenues of research that may be fruitful in meeting the above objectives and in solving some of the disease problems. The following discussion highlights research approaches that merit particular emphasis. A few of these studies, already underway, are still in their infancy. Others are not yet begun. Such studies should be vigorously pursued to fill in the gaps in knowledge regarding the prevention, diagnosis, and treatment of retinal vascular disorders.

Fundamental Studies

Regional Differences in Anatomy and Pathology

Diabetic retinopathy tends to be most pronounced at the center of the retina (posterior pole of the eye); peripheral areas are relatively spared. Similarly, diabetic retinopathy mainly affects the retinal circulation; it generally spares the choroidal blood vessels. The reason for this discrepancy is not known. Careful, comparative anatomic studies of normal and diabetic retinas may yield clues to explain these predilections—clues that could help explain the nature of diabetic retinopathy itself.

Physiological Studies

How is blood flow to the retina and choroid controlled? How can these separate flows best be measured by noninvasive methods? In this respect, the further perfection of two-point fluorophotometry and Doppler velocimetry should be encouraged. It is important to understand the hemodynamic factors that explain why the macular capillary system is predisposed to failure exemplified by edema, microcysts, and microaneurysm formation. Physiological studies of the choroidal circulation are of particular importance since so little is known about it. Aside from blood flow measurements, reliable, noninvasive methods should be developed to make the measurement of retinal and choroidal blood oxygenation a practical, everyday clinical method. Additionally, more extensive research use should be made of isolated perfused eyes; factors affecting ocular circulation can be studied separately and more easily modified in such preparations than in a living animal.

Permeability Studies

One of the earliest changes in diabetic retinopathy is the loss of integrity of the retinal capillaries. When this happens, unwanted fluid leaks into the surrounding retina. Fluid leakage, particularly when it occurs in the macular region, is a major cause of loss of reading vision in diabetic retinopathy and branch vein occlusion. Why some persons develop these vascular permeability changes and others do not still is not understood. The changes in permeability in retinal vessels should be compared to changes in the choroidal vessels and to changes in the vessels of the brain. It is striking that there is no recognized cerebral vasculopathy paralleling diabetic retinopathy. The reasons for this should be investigated. It is certainly well-established that the retina is part of the brain (see Chapter 11, *Retinal Organization and Visual Adaptation*) and that the blood-retina barrier is analogous to the blood-brain barrier.

The mechanisms underlying deleterious changes in vascular permeability must be investigated in order to develop methods for preventing or reversing them. In this regard, there are indications in other parts of the body that certain drugs can alter blood vessel permeability. It is important to try to find whether deleterious permeability changes in the eye can also be modified by drug therapy. Similarly, it is urgent to refine noninvasive methods of detecting minute changes in the permeability of retinal blood vessels in order to diagnose such conditions at an early stage.

There are also substantial opportunities for productive research with newer anatomical techniques. It is known that in the normal eye, the individual cells that make up the wall of small blood vessels in the retina form a tight seal one to another: they are joined in a special way by a recognizable and characteristic structure called a tight junction. Tight junctions can be visualized by several anatomical techniques, perhaps best by the recently developed freeze-fracture technique. Frozen tissue is fractured, and after special treatment the fractured surfaces can be visualized with the scanning electron microscope. It would seem reasonable to compare normal and affected retinas to see if there is a difference in cell junctions.

The walls of retinal capillaries are made of endothelial cells and basement membrane. Biochemical studies of the basement membrane of retinal capillaries also are of great importance because such studies could uncover the mechanisms of certain vascular diseases of the retina. Comparable studies of the lens capsule which are already underway have been productive.

Angiogenesis Factors

The stimulus which sets off retinal neovascularization is unknown. It is possible that a retina affected by vessel closure produces a substance that initiates new vessel growth. An analogous substance has recently been detected in solid tumors.[41] The effect of this tumor angiogenesis factor on the retinal vessels should be studied, for it may provide clues to mechanisms of abnormal retinal vessel growth. Inhibitors of blood vessel growth, such as that recently discovered in relation to the tumor angiogenesis factor, also merit extensive investigation.

In addition, pilot studies suggesting that an inflammatory reaction to insulin may produce retinal neovascularization also merit further investigation.[42]

Blood Studies

Pathologic clotting of the blood occurs in diabetes mellitus. The role of this change in diabetic retinopathy should be studied. Drugs that could influence pathological clotting also need to be investigated.

Basic Studies

Most important of all, the pathogenic mechanisms responsible for blood vessel abnormalities in virtually all types of retinal vascular disease remain unknown. Basic studies should be encouraged in order to investigate the responsible mechanisms in diabetes mellitus, hypertension, and other conditions leading to aneurysm formation, increased vascular permeability, and vascular occlusion. For example, a metabolic abnormality of the retinal vessels or retinal neurons must be sought which, if corrected, could prevent the initial and subsequent vascular abnormalities. Prevention, were it feasible, would be preferable to any treatment presently available.

Moreover, understanding must be sought of the deleterious train of events that follows vascular occlusion. In this regard, the development of an experimental means to occlude retinal blood vessels in laboratory animals[43] is of great importance and would make possible the search for locally-produced agents which incite new blood vessel formation.

Comparative Pathological Studies

Studies of blood flow, blood oxygenation, blood clotting, and other properties of the blood in normal individuals as compared to diabetics should be encouraged, especially for the early stages of diabetic retinopathy. It may be that a fault in blood flow calls forth the sequence of events common to several vascular retinopathies.

Enzyme and Tissue Culture Methodology

Biochemical studies of isolated tissues and cells offer much promise. Tissues from normal and diabetic humans or animals can have tremendous value in clarifying the mechanisms that may be responsible for the development of small vessel occlusions and leakage. For example, it is now possible to isolate in relative purity capillaries from the retina. These small retinal blood vessels, when isolated and grown in tissue culture, appear to retain some of the biochemical properties they possess in life.[44] As a result, it has recently become feasible to study the metabolic properties of retinal blood vessel cells. Of special note, certain enzyme

systems that have been associated with the development of diabetic complications in other parts of the eye, namely the lens, can now be investigated in retinal capillaries. (See report of the *Cataract* Panel, Chapter 3, *Diabetic Cataract.*)

Clinical Studies

Natural History

Disorders such as diabetic retinopathy,[39] branch vein occlusion, and sickle cell disease[45] each have quite variable effects on the retina. Some persons become blind within months, whereas others experience little if any visual difficulty. To study the effectiveness of a proposed treatment, one must first know what will happen without the treatment. Careful clinical documentation is important. The gathering of such data for retinal vascular diseases is not a simple matter; it requires the precise periodic examination of an affected individual for many years. On occasion, such knowledge of natural history provides clues regarding disease causation. For example, it is now widely recognized that new vessel growth usually follows retinal blood vessel occlusion. This observation led to the suggestion that ischemic retinal tissue might produce a substance which stimulates new vessel growth.

Design and Evaluation of Treatment

The previously listed basic laboratory and clinical studies form the core of a rational search for the information requisite for the design of a treatment of vessel leakage, vessel occlusion, and neovascularization.

All retinal vascular diseases have varying effects on vision. Because of this variability, it is often quite difficult to determine whether or not a given treatment is beneficial, and if so, to what degree. One important method for scientific evaluation of treatment is the randomized, controlled clinical trial. Such a careful, unbiased study of treatment versus no treatment, both studied simultaneously, is often the only way a meaningful evaluation can be obtained.

The collaborative Diabetic Retinopathy Study still in progress is one example of the type of careful and extensive investigation required in studying the evaluation of a treatment modality. The success of this Study to date in demonstrating the value of photocoagulation for certain stages of proliferative diabetic retinopathy justifies its continuation and its extension for similar evaluation of treatment for neovascularization due to other etiologies such as that associated with branch vein occlusion, central vein occlusion, retrolental fibroplasia, or sickle retinopathy.[43]

In addition, medical treatment of diabetic retinopathy and other retinal vascular diseases should also be evaluated. The potential usefulness of aspirin and related compounds and of hormonal treatment (such as suppression of growth hormone) merits special attention.

Because retinal photocoagulation is useful in the treatment of certain forms of diabetic retinopathy and of other vascular disease, it is important to develop a photocoagulation technique that is fully reproducible, optimally effective, and safe.

Priorities and Recommendations

- Compare differences in the anatomy and pathology of retinal blood vessels in different regions of the retina

- Conduct physiological studies on factors influencing blood flow, mechanisms of edema formation, closure of capillaries and large blood vessels, and protein transport into and across the neural retina
- Search for angiogenic substances, antagonists, and inhibitors
- Study biochemical abnormalities of diabetic retinas obtained from donor eyes and animal models
- Elucidate clotting mechanisms in diabetic retinopathy and other vascular and circulatory disorders
- Discover how the permeability of retinal blood vessels and pigment epithelium cells is controlled
- Study how normal blood vessel structure is maintained, how tight junctions form, and what factors are necessary for them to remain functional
- Investigate the metabolic relationship of neurons and glial cells
- Determine how the retina is maintained under conditions of stress, specifically, how and to what extent the retina tolerates ischemia, hypoglycemia, and other derangements
- Initiate additional clinical investigations of retinal vascular diseases
- Design and evaluate new methods of treating these conditions

The above priorities reflect the Panel's firm conviction that effective prevention, control, and cure of retinal circulatory disease will follow naturally from careful laboratory investigations. As an illustration, we discussed in an earlier section the role of basic studies of fluorescein angiography and photocoagulation technology in bringing about the presently established efficacious management of certain stages of proliferative diabetic retinopathy. To our minds, the basic laboratory research approaches listed above give substantial promise of yielding worthwhile improvements in clinical diagnosis and treatment in the years to come.

Resource Requirements

Each of the above recommendations should be pursued through the traditional mechanisms of research grants, center grants, and research contracts together with appropriate support for predoctoral and postdoctoral fellowships. Additional requirements are outlined in the tables at the end of this Panel report, bringing estimated total funding of this subprogram in FY 1978 to $10,064,000.

Research Grants

There are approximately 40 grants for research in *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities* in FY 1977. If we are to take advantage of the opportunities presently available to us, 33 additional new research grants need to be funded in FY 1978.

Specialized Clinical Research Center Grants

These grants are important; they support the efforts of a set of investigators, often from different disciplines, all of whom are focusing on a common research problem. An example of the type of approach made possible by this mechanism is the development of improved retinal photocoagulation therapy by teams made up of physicists, physiologists, and clinicians.

In FY 1977 the NEI supports two broadly-based, multidisciplinary clinical research programs funded by specialized clinical research center grants in retinal and choroidal diseases. We estimate that about one-third of this effort is directed toward retinal vascular and circulatory diseases. Three additional specialized clinical research center grants are merited, both by need and opportunity, for research in retinal vascular and circulatory diseases alone.

Research Contracts

In FY 1977 an estimated 53 research contracts will be awarded in this subprogram, including 17 for the collaborative Diabetic Retinopathy Study (DRS) and 15 for the collaborative Diabetic Retinopathy Vitrectomy Study (DRVS). As the results of the DRS have clearly demonstrated, a well-controlled, well-designed clinical study can yield significant benefits in preventing blindness. Although fully cognizant of the cost of such efforts, we recommend that an additional collaborative study requiring three additional contracts be funded in FY 1978 for research on the natural history and management of retinal vascular disease.

Training Fellowships

Predoctoral and postdoctoral training fellowship support must be expanded to meet the needs of the future. We recommend that predoctoral and postdoctoral fellowships be made available, and we strongly recommend that support be offered for one-, two-, and three-year periods. In FY 1976 there were only three NEI-funded postdoctoral fellowships in this field at an average annual cost of $12,000. The need for expansion is clear. Twenty-five such fellowships should be made available in the United States each year. To support a minimum of 25 fellowships, an additional allowance of $300,000 should be made.

3

Myopia

MYOPIA, OR NEARSIGHTEDNESS, is the inability to see distant objects in focus as the result of rays of light converging in front of the retina. This can happen if the cornea and lens bend the light rays too much (refractive myopia), but more frequently it is the result of the eyeball being too long (axial myopia). See Figure 4.

At birth, the eyeball is relatively short, and as a consequence, most young children are farsighted until four to seven years of age, when the growing eyeball lengthens to relatively normal adult proportions. In axial myopia, the eye lengthens excessively, especially during adolescence. Since this period coincides with school age, excessive use of the eyes for near work has been suggested as the cause of myopia; however, this theory is in dispute.[40-49] It is generally accepted that genetic factors largely govern the growth of the eye; the effects of use or other environmental factors are considered additive.

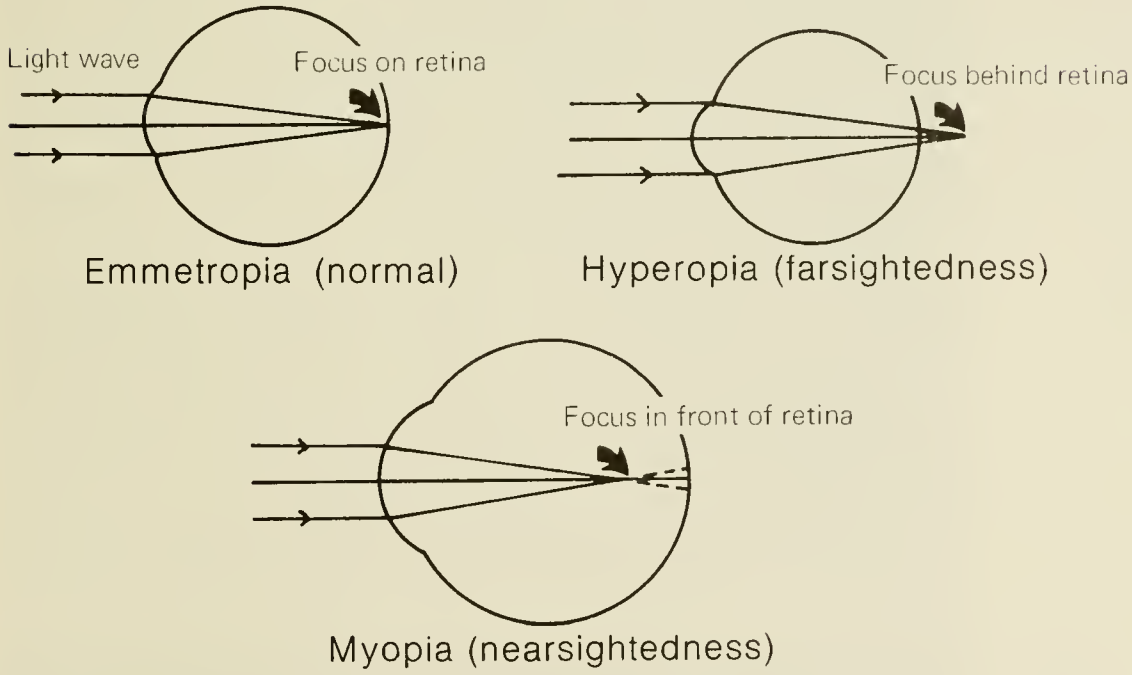

Figure 4. Refraction in the normal eye compared with hyperopia and myopia.

Myopia is certainly common: about one-third of all adults in the United States, more than 70 million people in total, are myopic.[50] Most of these people have simple myopia, a condition in which vision can be readily corrected with eyeglasses or contact lenses providing clear vision for distance. However, myopia is not without penalty. In addition to the psychological problems that occur in some young people when fitted with eyeglasses, the annual cost in the United States of eyeglasses and contact lenses to correct myopia is estimated to be over $1 billion a year.*

Of greater importance are the 700,000 myopes with imperfectly correctable vision, especially the 36,000 cases of severe visual impairment caused by this disorder. Even worse, about 10 percent of those with visual impairment will develop degenerative changes in the retina, choroid, and sclera, a condition known as pathological, degenerative, or progressive myopia. This condition can lead to irreversible loss of vision.

In progressive myopia the sclera (the white outer coat of the eye) stretches considerably, particularly at its posterior pole, producing a posterior staphyloma. Stretching of the sclera leads in turn to choroidal and retinal stretching, again at the back of the eye. At the same time, the vitreous gel degenerates and liquefies, traction bands form within it, and the bands then attach to and pull on the retina. Blindness occurs from incurable retinal detachment or from deficient circulation of blood to the stretched choroid and retina.

Accomplishments

Although myopia has long been of interest, productive research in this field is really just beginning.

Recently, three different research groups have claimed the arrest or partial regression of myopia in a high percentage of cases by the continuous use of locally applied atropine.[51-53] Atropine (belladona) and atropine-like drugs relax the focusing ability of the eye and dilate the pupil. Atropine may, in addition, have other unknown effects. These studies have been conducted with children at the age when myopia is rapidly increasing. Because these studies were from only one to four years in duration, it is not known whether the treatment had any lasting benefit, and therefore the results have not been widely accepted.[49] Experimental myopia has also been induced in monkeys forced to use their eyes for near vision for prolonged periods of time.[54] Interestingly, the developing myopia was stabilized after application of atropine to the eye.[55]

A different but equally fascinating clinical finding that hints at an anterior segment-posterior segment regulatory effect concerns ocular development in aniridia, a rare congenital anomaly in which the iris fails to form properly. Although usually complicated by a series of other pathological entities such as cataract and glaucoma, a recent study reported on a family with aniridia in which the other structures of the eye were normal.[56] Of interest in the present context, each member of the family was farsighted. Although a single case report must always be interpreted with caution, the nature of the refractive error in this family is certainly sufficient reason to pursue further studies along these lines.

Recently, an exciting new laboratory model for myopia has been discovered by scientists supported by the National Eye Institute who found that

*The Federal Trade Commission estimates that 100 million Americans wear corrective lenses and that $1.8 billion is spent on them each year. If 70 percent (70 out of 100 million) of these people are myopic, then the amount spent on corrective lenses for myopia can be assumed to be about $1.26 billion.

nearsightedness can be induced in macaque monkeys,[57] tree shrews,[58] and cats.[59] When the eyelids of one or both eyes were surgically fused in newborn animals, a progressive myopia resulted. In the monkey, this severe ("high") myopia did not depend upon changes in corneal curvature. Instead, the eyes increased in length, an average 15 percent greater after 1.5 years of lid fusion in the monkey. See Figure 5. Interestingly, the myopia became stationary after the eyelids were opened. This research raises questions both about the induction of myopia and the control of the growth of the eye, especially growth which produces a measurable change in refractive error.

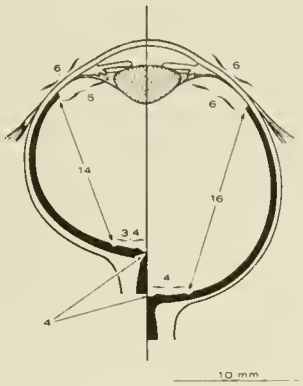

Figure 5. Effects of neonatal lid fusion on eye dimensions. The temporal half of a normal monkey eye (left) is compared with that of an eye in which lid fusion was performed.

A quite separate but equally pertinent observation is that glaucoma in the young frequently leads to enlargement of the eye and thus to axial myopia.[60] It is for this reason that clinicians are careful to test the intraocular pressure of children in whom myopia is progressing rapidly. Again, a laboratory model is available for this type of myopia because rabbits with congenital glaucoma also develop myopia secondary to lengthening of the globe.

In part, each of these observations may recapitulate events that take place during formation of the eye in utero. Long before postnatal events can exert any influence on its form, the eye's basic geometry has been molded during prenatal life; chief among the responsible factors are the differentiating tissues of the developing eye.[61] For instance, it has long been known that the enlargement of the embryonic eye is powered by the accumulation of vitreous substance within it. It is also known that the precise form the eye takes depends in part on the timetable and spatial distribution and differentiation of tough scleral tissue from soft prescleral tissue which envelops the embryonic eye.

Recently, it was demonstrated that the tough sclera is induced from its soft precursor by the pigmented epithelium of the retina.[62] Hence, untoward genetic or environmental influences on pigmented epithelium can lead to a disturbance in the form of the eye. As yet, knowledge of the tissue interactions responsible for ocular development is fragmentary. There is both need and opportunity to discover the mechanisms which mediate such interactions and to find the exact times during ocular development when such interactions are at maximal hazard to maladaptive genetic or harmful environmental influence.

Thus, several distinct clinical and laboratory findings exist to set the stage for investigations into the causes, prevention, and therapy of myopia. Given the frequency of myopia in the population and the substantially increased incidence of retinal detachment and macular degeneration in patients with high degrees of

myopia, it seems imperative that substantial efforts be put into investigations in this area.

Research Objectives

- Uncover the causes of myopia and other refractive disorders
- Find means of preventing myopia
- Explore new treatment methods

Research Needs and Approaches

If pathological myopia is to be understood, the normal functioning of the sclera and vitreous must be better understood. Only then can the changes occurring in progressive myopia be compared to the normal function of sclera and vitreous.

Study of the Normal and Abnormal Sclera and Vitreous Body

The sclera is a collagenous membrane which normally contains the intraocular structures forming a tunic against which the intraocular pressure is exerted. Under normal circumstances the scleral membrane resists stretching; but in high myopia, the sclera, choroid, and retina do stretch. When stretching occurs, the volume of the vitreous gel must expand considerably.

It is possible that abnormal development of the sclera is not due to a primary defect in this membrane, but to a deficiency in the choroid, retina, or vitreous. This would be analogous to poor development of sclera in the region of a chorioretinal coloboma. However, high myopia could as well be the result of an error in the structure of the sclera or in the control of its growth—a developmental deficit with lifetime consequences. Whatever the nature of the defect, it must be defined. Research on the normal and abnormal development of the sclera must be expanded.

Finally, changes occurring in the vitreous body are of prime importance because they frequently lead to retinal detachment in highly myopic eyes. Here again, the normal morphology and functioning of this tissue must be studied further in order to understand the changes occurring in high myopia (for greater detail, see Chapter 9, *Vitreous Humor).*

Experimental Myopia in Animals

How eyelid fusion induces myopia in laboratory animals is not clear. Further research is needed to determine how myopia can be predictably and regularly induced by lid fusion in order to explore the actual mechanism of eye enlargement and to ascertain whether other ocular changes (e.g. retinal degeneration) occur just as they do in patients with severe myopia. Monkeys are particularly appropriate experimental subjects because their eyes are so similar to those of humans.

Clinical Research in Myopia

In the past, clinicians have tried various forms of treatment for myopia.[49]

Medical Approach

In the last few years, there have been several reports that prolonged, daily use of atropine drops can retard the development of myopia.[51-53] Undoubtedly, if correct, these findings would be of great clinical importance. However, these findings have not been widely accepted; in fact, the whole question of the value of atropine treatment is shrouded in controversy.[49] After careful study, the Panel believes the matter to be of sufficient importance and the reported studies to have shown enough promise to warrant substantial further emphasis. Specifically, controlled, well-designed clinical studies should be initiated to determine the value of atropine or other mydriatics in arresting the progress of myopia. Such studies should cover the full duration of human eye growth.

Surgical Approach

It is understood that surgical approaches, at least those presently available, are probably only palliative. They are justified only as a last attempt to prevent impending blindness. It is clear that the prevention of the ravages of high myopia awaits a better understanding of pathogenesis.

Two surgical approaches for severe progressive myopia have been attempted: resection of the thinned sclera and reinforcement of the thinned areas with donor tissue. Studies of these approaches have often been poorly controlled and the results inadequately documented. These procedures should be perfected in laboratory animals; thereafter, their worth in humans should be carefully documented and evaluated.

It appears indispensable to study first the properties of the normal sclera. As already mentioned,[60] it is known that the sclera in the young stretches more easily (under the influence of raised intraocular pressure, for instance) than in the old. The morphology, including fine structure, and the biochemistry of the normal sclera should be studied in detail and the relationship between structure, composition, and stretching investigated. Findings in normal eyes should be compared to those in eyes with high myopia.

Since myopia is often hereditary (or may be associated with hereditary conditions such as in the Marfan's and Ehlers-Danlos syndromes), it is possible that an inborn error may exist in the structure of ocular collagen or in one of the enzymes that regulate and maintain the production of normal collagen.

This type of research will be aided by the fact that specimens of sclera are relatively easy to obtain from humans.

Priorities and Recommendations

- Undertake a series of thorough morphological and biochemical studies comparing the sclera from the normal and myopic eyes.
- Investigate scleral rigidity.
- Study the psychophysics of the retina in myopia, especially for evidence of photoreceptor disorientation.
- Seek animal models for the study of the mechanisms and treatment of myopia and other degenerative disorders.
  - Fully explore the eyelid suture model of induced myopia in the monkey.

- Search primate colonies for monkeys with hereditary forms of myopia. It is already known that some monkeys are extremely myopic.[63] When such animals are located, a colony should be founded where they can be selectively bred for distribution to vision scientists.

- Conduct carefully-documented natural history studies of myopia and other related degenerations, including studies of the effects of nutrition, endocrinological relationships, and cultural factors.

- Conduct carefully designed clinical trials in humans to determine the effectiveness of atropine-like eyedrops in slowing or preventing the development of simple myopia and progressive myopia.

Resource Requirements

There are currently no grants funded by the National Eye Institute aimed directly at the study of myopia or related disorders of the retina. The first experimental findings on myopia in lid-sutured monkeys were incidental to other studies supported by the National Eye Institute.

The research activities recommended by the Panel require 15 new research grants and three contracts. Estimated total funding necessary to support research in this subprogram for FY 1978 would be $1,710,000.

Under contracts recommended in Chapter 12, *Special Areas of Future Interest,* monkeys with different forms of myopia should be sought out and bred. At least one project should be dedicated to a survey of large primate colonies in a quest for myopic monkeys.

With regard to the controlled clinical trials recommended, a commitment should be made to provide long-term support for at least two well-designed, long-term treatment trials.

It will also be necessary for the National Eye Institute to encourage manpower training in conjunction with laboratory studies of myopia. Only in this way will it be possible to develop the skills and expertise necessary to take advantage of future research developments. Individual vision researchers must be trained not only in such practical clinical skills like retinoscopy, keratometry, and ultrasound, but also in basic research disciplines. Each training program should be designed for the individual. Major present needs are for those with training in developmental anatomy, biochemical genetics, and physiology.

For a summary of resources required for this subprogram, see the tables at the end of this report.

4

Tumors

TUMORS OF THE EYE arise principally from the retina and the uvea, although some originate from other areas such as the lids, the conjunctiva, and the orbit. Eye tumors have an importance that surpasses their frequency. Not only are they a cause of blindness, they can cause death as well. Even with radical surgery to remove the tumor, metastasis is common. For example, the five-year mortality rate for ocular melanomas in one recent report was 60 percent.[64]

Retinoblastoma

Retinoblastoma is the most common ocular tumor occurring in children; it rivals neuroblastoma as the most common congenital tumor of any type. Various studies in the United States and Western Europe in the last 40 years have indicated that retinoblastoma occurs in an average of one in 23,000 live births. A disquieting feature of retinoblastoma is that its frequency appears to be increasing.[64,65]

The frequency may well be higher in other parts of the world than in the United States and Western Europe. For instance, a review of the prevalence of retinoblastoma reveals that during a two and one-half year period in Nigeria, there was one case of retinoblastoma for every 192 patients examined.[66] After reviewing other hospital series, it was also learned that in Nigeria the incidence is much higher among Nigerian children than among European children. Nearer to home, the estimated frequency of retinoblastoma in a recent study in Haiti was calculated at one in every 3,300 live births.[66]

The costs to the individual and to society of patients with retinoblastoma are high. Although these tumors can be treated with up to 90 percent effectiveness, they are often bilateral and generally occur within the first three years of life. The management of retinoblastoma may involve the use of various therapies: two types that treat the entire retina (radiotherapy and chemotherapy) and several that treat local areas of the retina [diathermy, radon seeds and ^{60}cobalt (^{60}Co) plaques, light coagulation, and cryotherapy].

Retinoblastoma victims whose tumors have been cured but whose vision has been lost present the same economic difficulties and social tragedies as do other victims of childhood blindness. In fact, children who have had retinoblastoma compose a significant portion of the population in schools for the blind.[64]

Malignant Melanoma

Melanoma usually occurs unilaterally with a devastating visual result. A significant number of patients develop metastatic disease from melanoma in which there is an agonizing terminal course. Although mortality statistics on intraocular tumors such as melanoma are incomplete, the American Cancer Society estimates that approximately 350 Americans die annually as a result of malignant melanoma arising in the eye. Statistics on the incidence, morbidity, and mortality of orbital and adnexal tumors are difficult to pinpoint, since these figures are diffused throughout a number of more general tumor categories.

Research Status

Knowledge of eye tumors is limited. Tumors can be diagnosed and attempts can be made to destroy them. By tissue examination, the tumor can be labelled and some assessment made of the patient's prognosis. However, there is almost total ignorance of the cause of ocular malignancies or how they develop. Consequently, except for genetic counseling to avoid the risk of retinoblastoma, it is not possible to prevent ocular tumors.

Problems in Diagnosis

Although the ability to diagnose and treat ocular tumors compares favorably with that for tumors elsewhere in the body, these procedures are still imperfect. Often it is difficult to tell whether a given intraocular mass is or is not a malignant tumor. Specific immunologic and biochemical tests are urgently needed for diagnosing malignant tumors of the eye—especially malignant melanoma of the choroid.

Problems in Treatment

Ophthalmologists disagree about the value of available treatments. Controversy exists because there have been no controlled studies of the effectiveness of radiation, laser coagulation therapy, and cryotherapy for certain intraocular tumors as alternatives to surgery. Disagreement is especially strong over the merits of local excision of tumors, both in the anterior and posterior portions of the eye, versus enucleation of the whole eye. The fact that it is not agreed whether enucleation actually improves the prognosis of the patient with ocular melanoma indicates how much still needs to be done in this area.[67-69]

However, whatever the current disagreement, the prospective value of "full-thickness eye wall resection" for melanoma of the choroid justifies careful development of surgical techniques in laboratory animals and, in certain selected cases (one-eyed patients), judicious, carefully-monitored clinical trials.[70]

One of the most worrisome concerns is how to treat patients after tumor removal and before the time—often many years later—that metastasis develops. Does the use of bacille Calmette Guérin (BCG) vaccine or 5-dinitrochlorobenzene (DNCB) improve or worsen the patient's prognosis?[71] There is considerable evidence that BCG may be an effective treatment of skin melanoma and less so for ocular melanomas. Other experiments indicate that hazards may exist as well. Again, more study is needed of the value and risks of such treatments in humans.

Once removed, melanomas, like most eye tumors, can be histologically labelled, but the relationship of certain histopathologic features, such as the size of the melanoma, to the patient's prognosis is still open to question.[67,72]

Critical microscopic study is still needed to answer such basic questions as whether there are differences between the familial (genetic) type of retinoblastoma and the apparently sporadic cases of this tumor.

Accomplishments

When ocular tumors are diagnosed early, death is often prevented. Treatment, however, frequently requires removal of the eye. Eye tumors are most often discovered after the victim notices that something is wrong and seeks professional attention. The ophthalmologist then diagnoses the presence of a tumor by a careful eye examination. Other good diagnostic methods are available; these include, for intraocular tumors (tumors within the eye) fluorescein angiography, ultrasound, ^{32}phosphorus (^{32}P) radioisotope techniques, and in selected cases, biopsy or tapping of the anterior chamber fluid for examination. For diagnosing tumors outside the eye, arteriography, venography, "CAT" or "EMI" scans (special X-ray techniques), and ultrasonography may be usefully employed.[72-74]

All of these techniques can help determine the nature and extent of a tumor. Several types of treatment are available; these include "watchful waiting," surgery, X-irradiation, laser or light coagulation, cryotherapy, chemotherapy, or in some instances, a combination of two or more of these treatments.[64,67,75]

Once the tumor has been removed, it is usually prepared for microscopic study and pathologic examination by which the degree of malignancy can often be determined and prognosis assessed.[72,75] In the case of retinoblastoma, other family members may be examined, and genetic studies and counseling may be carried out.[75]

Research Objectives

- Improve methods of diagnosis
- Determine the cause or causes of ocular tumors
- Evaluate methods of treatment

Accomplishment of these objectives promises to benefit patients who suffer from ocular tumors by saving lives, by alleviating visual loss, and by lessening physical and emotional suffering.

With a well-designed, properly directed, and adequately funded program to study ocular tumors, major advances in diagnosis can be expected. For example, it should be possible to establish the comparative usefulness of some presently available diagnostic techniques, such as ^{32}P and immunologic tests. It should also be possible to determine which are the most effective treatments presently available and how and when they should be applied. The usefulness of BCG injection following removal of the ocular tumor should be determined. In addition, further knowledge of certain features of eye tumors such as the development of the photoreceptor elements in retinoblastoma, catecholamine production by retinoblastoma, and tumor angiogenesis factor production by melanomas may give insight into the biological nature of such tumors.

Working toward these research objectives also promises to benefit ongoing research on tumors in general. Compared to other organs subject to tumors, the eye offers unparalleled opportunities for observing, approaching, and isolating

the tumor. The knowledge acquired about the etiology, pathogenesis, morphology, diagnosis, treatment, and epidemiology of eye tumors may well have important implications for other human cancers.

In addition, it should be noted that the eye is a frequent site for tumor metastasis. As such, it affords an invaluable chance to measure precisely the visible effects of different types of systemic therapy.

Research Needs and Approaches

In FY 1977 NEI is supporting nine studies which deal primarily with ocular tumors. Four additional studies have significant "secondary" implications for eye tumors. Although the federal government has substantially increased general support for cancer research, we believe that direct support should be provided for studies of eye tumors in particular. These studies should involve ophthalmologists and visual scientists who are trained in the basic science and clinical problems of eye cancer.

At present, the most promising lines of research involve:

- The search for a viral etiology in ocular tumors
- Immunologic studies to improve diagnosis, surveillance, and treatment of ocular tumors
- Epidemiologic studies regarding the diagnosis and treatment of ocular tumors

Viral Etiology

In 1975, understanding of the genetic process was revolutionized by the discovery that ribonucleic acid (RNA) can pass information to deoxyribonucleic acid (DNA).[76] This finding demolished the idea that DNA always passes information to RNA and never the other way around. The research which led to this discovery was largely motivated by a quest to understand how viruses cause cancer. When a cell becomes malignant, its genetic material goes awry, and it begins to produce abnormal descendants. It was shown how an invading RNA virus could transform cells so that their descendants showed influences of the virus as well as of the original genetic material. The key to how viruses interact with hereditary material in cells is a viral enzyme known as "reverse transcriptase." This enzyme has been found in virtually all RNA tumor viruses and has recently been found in retinoblastoma and in other malignant tumors of the eye.[77]

Tumor viruses previously thought of simply as infectious agents are now recognized as units of genetic information that may be passed horizontally or may have been incorporated into the cell millions of years ago to be activated by a second factor. The role of reverse transcriptase in ocular tumors and its possible indication of the presence of a virus is thus a promising lead, one that must be vigorously explored.[72]

In recent years, evidence has accumulated that suggests that viruses play a role in the etiology of many types of human cancers. In tumors studied by electron microscopy, there are frequent reports of virus-like particles.[78] These usually involve two general types: an RNA tumor virus group and the DNA herpes virus. Evidence for the classification of RNA tumor viruses is far from complete, but they are generally grouped together because they look alike and because several representatives have been shown to contain RNA. According to their

morphology by electron microscopy, they are commonly referred to as type A, B, or C particles. Collectively, these are usually referred to as oncorna viruses.

The second type of virus-like particle reported in some spontaneous tumor cells is the DNA herpes virus. Herpes-like inclusion bodies have been noted in the cornea and limbus of the eye. The oncogenic potential of ultraviolet-light inactivated herpes simplex virus (Types 1 and 2) has been convincingly demonstrated. Burkitt's lymphoma, a tumor that has many features in common with retinoblastoma, is associated with a herpes-like virus known as the Epstein-Barr (EB) virus. At present, however, it is not known if the EB virus or other herpes viruses cause human cancer.

A third group of viruses, widely studied for its possible role in causing human cancers, is the oncogenic DNA viruses, which include polyoma virus, simian virus 40, other simian viruses, and a number of adenoviruses. Polyoma virus and simian virus 40 are members of the viral group (papovavirus) that causes human warts and papillomas. Ophthalmologists are familiar with the adenoviruses as causative agents for pharyngoconjunctival fever and epidemic keratoconjunctivitis. These oncogenic DNA viruses cause signs of malignant transformation in a variety of mammalian cells grown in vitro. The injection of such cells (i.e. transformed in vitro) into a host of the same species is followed by the development of a malignant tumor at the site of inoculation with consequent invasion and metastasis by the tumor.[74] It is yet to be established whether such DNA virus-induced malignancies actually occur in nature. A number of experimental malignancies have been induced both in vivo and in vitro using the viruses discussed above.[78-80]

An important finding that is being explored further is the abnormality of one of the D chromosomes (probably number 13) in retinoblastoma. More than 25 percent of patients reported with this abnormality have retinoblastoma.[81] All patients described in the literature with the long arm of the number 13 chromosome deleted also are mentally retarded. Apparently, only a relatively small percentage of retinoblastoma cases are caused by a gross chromosomal abnormality. It is possible that a more subtle defect causes the majority of cases. It has long been known that viruses together with many other agents will induce chromosomal abnormalities. Chromosome abnormalities of adenovirus 12-induced tumor cells are currently being compared with human retinoblastoma cells. Immunologic techniques are also being used to explore possible evidence of adenovirus induction in human retinoblastoma.

Immunologic Studies

Immunologic studies to diagnose, monitor, and treat ocular tumors are being pursued in several laboratories. For instance, it has been shown that cutaneous delayed hypersensitivity responses to crude membrane extracts of a tissue culture line derived from retinoblastoma occur in retinoblastoma patients.[82] The same study also found cell-mediated immunity to this cell line utilizing the ^{125}I-iododeoxyuridine cytotoxicity assay in vitro. Interestingly, retinitis pigmentosa patients may demonstrate a similar response.[83]

In the same vein, another group of investigators recently studied the cutaneous delayed hypersensitivity response to a soluble melanoma antigen and reported that it shows promise as a diagnostic aid.[84] Leukocyte migration inhibition assays also indicate that patients with choroidal melanoma have cell-mediated immunity to common melanoma-associated antigen. Others have also reported a possible relationship of tumor-associated antibodies in the serum of patients with intraocular malignant melanomas.

In summary, approaches to understanding the etiology and pathogenesis of ocular tumors should include a search for a possible viral etiology. The complexity

of the problem warrants a multidiscipline approach utilizing the knowledge and skills of morphologists, molecular biologists, enzyme chemists, immunologists, and virologists. Such units could study both human and animal tumors. An intense, broad-based, immunologic investigation for the presence of tumor-specific antigens and resultant antibodies in tumor patients is also warranted. The presence and specificity of various immune mechanisms are of increasing importance, both for diagnosis and treatment of ocular tumors.

Epidemiologic Studies

A coordinated, cooperative study to evaluate methods for diagnosis and treatment of ocular tumors, combining the prospective and retrospective experience of the country's major ophthalmic centers, would be useful.

Diagnostic Studies

Ultrasound evaluation of ocular melanomas is also being pursued. Other workers have markedly improved the accuracy with which ^{32}P can be used in the diagnosis of melanomas. Investigators have pointed out in detail the usefulness of fluorescein angiography in the differential diagnosis of intraocular tumors.

Priorities and Recommendations

The present deficiencies in the research effort on ocular tumors have many roots. What is needed is a planned, thoughtful, multidiscipline, coordinated approach to ocular tumors ranging from basic science to clinical application. Taking these conditions into mind, the Panel's specific recommendations are as follows:

Etiology of Ocular Tumors

- Investigate further the role of reverse transcriptase in retinoblastoma and melanoma, and correlate these findings with the presence and template specificity of this enzyme in the developing retina and pigmented tissues of the eye.
- Search for a virus in ocular tumors, particularly in retinoblastoma and melanoma, utilizing a multidisciplinary approach including correlated morphologic, biochemical, virologic, and immunologic studies.
- Conduct a widespread search for a spontaneous animal model of retinoblastoma involving both a retrospective study of materials on hand at major veterinary pathology repositories and a prospective study involving veterinary ophthalmological studies of wildlife, animals in zoos, domestic animals, and pets.
- Establish animal models of retinoblastoma and melanoma using various species-specific DNA and RNA tumor viruses.

Pathogenesis of Ocular Tumors

- Determine the cells of origin of retinoblastoma and malignant melanoma.

- Study tumor angiogenesis factor or other angioproliferative factors and their role in the growth of retinoblastoma and melanoma, particularly their role in spontaneous regression of retinoblastoma.
- Clarify the relationship between calcification and spontaneous regression of retinoblastoma.

Histologic Studies

- Reevaluate the classification of retinoblastoma and its prognostic implications. Perfect the classification on an ultrastructural basis.
- Evaluate the relation of size of the tumor to cell type and prognosis.
- Establish an ocular tumor registry, including facilities for tumor preservation (e.g. deep-freeze).

Diagnosis of Ocular Tumors

- Conduct a collaborative clinical study to determine the accuracy and limitations of the use of ^{32}P for the diagnosis of ocular melanoma.
- Develop and standardize reproducible techniques for tumor measurement.
- Determine the presence of specificity of tumor-related circulating antibodies and cell-mediated sensitivity to ocular tumors.
- Develop and evaluate a safe skin test for the diagnosis of retinoblastoma and of malignant melanoma.
- Use paracentesis to search for melanin precursors in melanoma and to search for isoenzymes of lactic dehydrogenase in retinoblastoma.
- Conduct definitive chromosomal and genetic studies, possibly using cell fusion techniques, to determine the presence of a chromosomal abnormality in retinoblastoma patients.
- Identify HLA antigens associated with ocular tumors as a means of chromosomal definition.

Treatment of Ocular Tumors

- Establish a tumor registry possibly comprising several major eye centers. This is the only way a statistically valid comparison of various treatment methods can be accomplished.
- Through this or other means, conduct a retrospective and prospective comparative evaluation of various methods of treating ocular tumors ranging from "conservative" watchful waiting to enucleation. Consider the inclusion of a study of local anterior excision and of posterior full-thickness excision.

- Conduct a comparative study of X-ray therapy, photocoagulation, cryotherapy, and other surgical methods.
- Evaluate the immunologic status of spontaneously cured retinoblastoma and melanoma patients, and attempt to transfer available immunologic factors to patients with active disease.
- Evaluate bacille Calmette Guérin (BCG) vaccine and 5-dinitrochlorobenzene (DNCB) as aids in treatment in malignant melanoma.
- Compare the effectiveness of various chemotherapeutic agents on ocular tumors.

Epidemiologic Studies

- Ascertain the incidence and frequency of various types of ocular tumors, their prevalence under various environmental conditions, and differences in their incidence and course in different ethnic groups.

Resource Requirements

In FY 1977 the NEI will fund approximately 11 research grants costing an estimated $712,000 for investigations of ocular *Tumors*. The greatly expanded research program recommended herein will require a considerable increase in support. The Panel's projection of the support required for this program in FY 1978 is displayed in the tables at the end of this report. The total estimated FY 1978 budget for ocular tumors amounts to $2,170,000.

This expanded program will also require new principal investigators. One of the major deficiencies of ocular tumor research carried out to date is that the basic research is being done by ophthalmologists with incomplete training in the pertinent basic disciplines. To achieve our objectives, we will need either to attract from other scientific disciplines or to train from within the eye research community four or five electron microscopists, four or five enzymologists, and similar numbers of virologists and immunologists, all interested in the biology of ocular neoplasms.

We recommend that the bulk of support be provided through individual research grants and through the establishment of two specialized clinical research centers. In addition, adequate research career development awards and fellowship awards should be made available to bring into the visual sciences the basic scientists required or, alternatively, to train ophthalmologists adequately in the necessary basic sciences.

5

Macular Diseases

DISEASES OF THE MACULA affect the central, high visual acuity area of the retina and lead in many cases to severe loss of vision. See Figure 6. It is estimated that each year over 165,000 people in the United States develop macular disease.[1] In some cases, this is of such severity as to cause legal blindness. For many others, it represents a lesser degree of impairment, but one in which the ability to read or to see small objects clearly is lost.

Figure 6. Simulated comparison of normal vision with vision in macular degeneration.

Macular diseases represent a complex group of conditions which can be outlined as follows:

- *Senile macular degeneration.* The most common form of macular disease occurs for the most part in the elderly who lose reading vision. The inability to read turns the retirement years into years of frustration for the affected individual.

- *Juvenile (hereditary) macular degeneration.* Macular degeneration occurring in individuals under the age of 20 severely limits the choice of a career and, indeed, can even hamper learning itself.
- *Central serous macular disease.* This recurrent disorder of the 20- to 40-year age group causes repeated episodes of blurred vision; after each attack the retina recovers to a variable extent.
- *Toxic macular disease.* The central visual area has a special susceptibility to the toxic effects of several different types of drugs.
- *Others.* There are numerous categories of macular disease which, although individually uncommon, taken together become a significant cause of blindness. These conditions include the macular degeneration that occurs in the presumed ocular histoplasmosis syndrome, trauma, angioid streaks, and membrane formation over the surface of the retina.

Other forms of macular disease such as those occurring with diabetic retinopathy and high myopia are discussed in other chapters of this report.

Accomplishments

There have been significant accomplishments in distinguishing the various categories of macular disease, in making clinicopathologic correlations, and in developing new techniques for diagnosis. New treatments for some forms of macular disease are now undergoing evaluation.

Descriptive Categorization of Disease

It is only in the last ten years that scientists have come to recognize distinct categories of macular disease. Prior to this time, macular diseases were categorized in a rather arbitrary fashion; for example, by age of onset as "senile" and "juvenile." We now know that there are several types of senile macular degeneration, each of which stems from a quite separate and distinct pathophysiologic mechanism. A new, improved classification is in the making based on progress in diagnosis.[85,86]

Clinicopathologic Correlations

The need for accurate descriptive categories led to a concerted effort to study eyes removed at autopsy with known, clinically-documented macular abnormalities. Through such correlative studies, it was learned, for example, that the devastating scar formation occurring in one type of senile macular degeneration follows the abnormal growth of new blood vessels inward from the choroid through Bruch's membrane. These new blood vessels lie under the pigment epithelium where they ultimately bleed, destroying the function of the retina.[87,88] From other such studies, it has been found that macular disease may be caused by abnormalities originating in the retina, the pigment epithelium, Bruch's membrane, or choriocapillaris.[88-90]

Diagnosis: Fluorescein Angiography

As described in Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities,* fluorescein angiography has proved an indispensable technique for

visualizing blood vessel abnormalities in the retina. In addition, this technique sometimes permits interpretation of abnormalities other than those of blood vessels; for instance, faults in the retinal pigment epithelium and Bruch's membrane are often visible.[32,33]

Treatment: Laser

The complex technological development of the argon laser has opened new possibilities for the attempted treatment of macular abnormalities. In selected instances, abnormal blood vessels may be closed off before they bleed, or breaks in tissue that permit the flow of blood components to unwanted areas may be sealed off.[91]

Research Objectives

- Understand the metabolic interrelationships among retina, retinal pigment epithelium, and choroid
- Discover the mechanisms that control new blood vessel growth in the choroid
- Find better methods of diagnosis and treatment

It is clear that the retina, the retinal pigment epithelium, and the choroid work together as a unit. A local failure of any of these tissues individually interferes with retinal function and produces a blind area. Some forms of macular disease are caused by primary abnormalities in the retina, some by primary abnormalities of the retinal pigment epithelium, and some are caused by abnormalities of the choroid. Thus, under the first objective, studies of this interdependent metabolism both in the normal and abnormal state must continue to be pursued. Particular attention must be given to altered metabolic function as a result of aging in order to understand the genesis of senile macular degeneration.

The second research objective is to understand the common and disastrous form of senile macular degeneration which occurs when new blood vessels grow from the choriocapillaris to an abnormal location underneath the retinal pigment epithelium.[92] Recent research advances indicate that new blood vessel growth arises from a specific stimulus. At least in malignant tumors, a specific biochemical stimulus incites the formation and continued growth of new blood vessels. It must be learned whether the same or a similar agent is at work in the eye. This discovery represents the best clue available for studies of abnormal growth of new blood vessels.[93] It also demonstrates the vast potential of basic research which truly does not obey parochial boundaries. Instead, progress in one area of cell biology often has broad ramifications.

The third research objective is to improve the diagnosis and treatment of macular disease. There is a special need for new diagnostic techniques to indicate the earliest pathological changes, particularly those that are harbingers of the more destructive types of macular degeneration. There is also a substantial need for improved therapy. This implies both the discovery of new medical agents and the perfection of technical methods such as laser photocoagulation. It requires the accurate evaluation of both. Better therapy and better diagnosis go hand in hand since the evaluation of a therapy's effectiveness depends in exact measure on the degree and precision of diagnostic evaluation of function.

Research Needs and Approaches

The Panel proposes two broad research approaches to meet the above objectives: new and enlarged basic laboratory studies and improved clinical studies. The specific needs to be met under each of these approaches are discussed below.

Basic Laboratory Studies

Anatomy—The Aging Process

Of primary concern are the anatomical changes in the retina, retinal pigment epithelium, and choroid which occur during the aging process. It is known, for example, that following certain changes in Bruch's membrane in the macular region, abnormal blood vessels can grow inward from the choriocapillaris to lie underneath the pigment epithelium. It is not known exactly when the new blood vessels begin to grow. Nor is it known precisely of what the age-related changes in Bruch's membrane are comprised.[88] An anatomical correlation of aging changes in Bruch's membrane with changes in the attachment area of pigment epithelial cells or with the precise form of the choriocapillaris could suggest etiologic mechanisms. The essential component of Bruch's membrane is collagen. This ubiquitous protein has been studied in great detail in other parts of the body, but little is known about the precise composition and metabolism of collagen in Bruch's membrane or about its changes with aging.

Predisposition of the macular region. It is well known that the macular region is predisposed to various degenerative changes, such as a degeneration of the retinal pigment epithelium. It is not at all clear why the macula should be so predisposed. We know that there are various specializations in the macular region, such as very high density of cones with elongated outer segments and a capillary-free area. A critical comparison of all differences between the central and peripheral retina may provide clues regarding susceptibility to various types of disease. Additionally, the existence of yellow pigment in the macular area needs to be studied. Its effect on visual perception and its possible role in protecting the macula against photic damage need to be investigated.

Clinicopathologic correlations. In the recent past, these correlations have made possible a more adequate categorization of macular diseases.[85-87,94] Data obtained from autopsy eyes with distinct macular abnormalities will continue to prove invaluable. For example, in central serous choroidopathy, it is not understood what abnormality of the retinal pigment epithelium permits fluid from the choriocapillaris to accumulate under the retina. It is only known that the barrier function is deficient. The application of recently developed techniques, such as scanning electron microscopy, or of already existing techniques to the problem of blood-retina barrier failure could well improve understanding of the anatomical abnormalities occurring in this disorder.

To apply modern research techniques to the study of macular degeneration, the present way in which postmortem and surgical eyes are obtained must be drastically altered. There is a need for a coherent plan of action in which eyes with specific types of macular pathology can be collected and distributed. They must be collected in such a way that the specific requirements of a given research protocol are followed, and a means of allocation and delivery must be devised to make it feasible for investigators to follow defined research programs.

Physiology—Retina-Pigment Epithelium Relationships

The physiologic dependence of the retina on the retinal pigment epithelium is presently under intensive investigation. Research on the role of the retinal pigment epithelium in maintaining rod and cone function and providing for the needs of the vitamin A metabolic cycle has yielded much-needed information regarding possible abnormalities which could cause macular disease. Further investigations, particularly including tissue culture studies of isolated cell lines, hold much promise; they will continue to improve understanding of these interrelationships.

Blood-retinal barriers. Substances circulating in the bloodstream do not have free access to the retina. Pigment epithelial cells are joined to one another by a shared intercell fusion known as a tight junction which prohibits the intercell passage of sugars, amino acids, proteins, and a variety of other substances. To enter the retina, all such substances thus need to pass through the pigment epithelial cell. Breakdown of this barrier at the macula is manifested clinically by abnormal accumulation of fluid under the retina with consequent focal retinal detachment. More information about how tight junctions are formed and what the requirements are for their maintenance during life is urgently needed.

Angiogenesis factor. It is now known that malignant tumors can produce a substance which induces new blood vessels to form.[93] There is reason to suspect a comparable mechanism may play a part in the production of choroidal neovascularization. If this is confirmed, a series of investigations to discover where and under what conditions such agents arise would be a natural follow-up.

Dye studies. Fluorescein angiography has made possible the study of faults in retinal blood vessels in clinical practice. Because of the role of the choroidal circulation in macular diseases, an equal capability is needed to visualize the choroidal circulation.[33] The projects presently underway in this field should therefore be encouraged. Special emphasis should be placed on the use of advanced technology, such as photofluorometry, to achieve improved results. In addition, a search for means other than marker dyes to measure blood flow and the state of the blood-ocular barriers should be encouraged.

Psychophysics. It is important to improve early diagnosis of defects in macular vision. Better means are needed to measure the visual response to a given visual stimulus in an objective way. For example, it has been shown that a very early sign of macular disease can be found in the careful determination of a patient's sensitivity to the color red. New measures are needed to test this sensitivity that will lessen the variability in responses in the same individual and that are precise enough to permit the type of accurate test-retest needed for critical evaluation of drug toxicity or of therapeutic efficacy. (See report of the *Sensory and Motor Disorders of Vision* Panel, Chapter 3, *Optical and Pupillary Disorders.*)

Electrophysiology. The electrical response of the whole retina can be studied in the living human subject by a simple and safe technique known as electroretinography. It is also known that local electrical changes may occur in the retina as an early sign of macular disease. Improved electroretinography techniques that can reliably detect isolated macular abnormalities merit further development.

Biochemistry—Aging

It is now possible to maintain individual cells from the retina, pigment epithelium, and choroid in tissue culture. The tissue culture environment can

then be manipulated in an attempt to duplicate abnormalities that lead to macular degeneration. In addition, efforts should be directed toward maintaining diseased tissues in culture to determine biochemical abnormalities.

Toxicology. Certain chemicals are known to lead to the destruction of the retina and/or the retinal pigment epithelium. How these toxic materials do their damage is not clear. The entire matter merits further investigation (see Chapter 12, *Special Areas of Future Interest).* In some cases the effects of toxic agents can have broad implications for understanding the etiology of macular degeneration.

Animal Models

A major stumbling block in the study of macular diseases is the inability to obtain diseased tissue by biopsy for anatomic, physiologic, and biochemical studies. The development of animal models of macular degeneration would provide significant new routes of investigation. For instance, a baboon at the Chicagoland Zoological Park with bilateral macular disease was discovered recently.[94] Intensive investigation of the entire colony revealed that several baboons were affected, that the condition involves the entire retina, and that it has several aspects indicative of a hereditary disorder. The opportunity for productive research both in pathogenesis and in treatment afforded by the discovery of such animals cannot be overemphasized. A widespread search of animal colonies throughout the world to find other types of retinal degeneration is fully warranted.

Clinical Studies

Natural History

The different types of macular degeneration are quite variable in course. As a result, it is imperative to develop an accurate classification of macular diseases and to find out as precisely as possible the typical clinical history of each type. This knowledge is requisite to any reliable evaluation of treatment. In addition, careful studies of natural history often provide clues to disease causation. For example, as a direct result of such studies, it is now widely recognized that subpigment epithelial neovascularization essentially never occurs in the absence of abnormalities in Bruch's membrane.

Design and Evaluation of Treatment

The previously listed basic laboratory and clinical studies form the core of a rational approach toward developing treatments of macular diseases. Crucial to the evaluation of treatment is the application of rigorous clinical research methodology; only a carefully constructed clinical trial makes a meaningful evaluation possible.

The ongoing collaborative Diabetic Retinopathy Study, supported by the National Eye Institute, is an example of a careful and extensive investigation of the worth of a treatment. The success of this evaluation justifies comparable clinical trials for macular diseases associated with subpigment epithelial neovascularization and for those macular diseases associated with a breakdown of the barriers which prevent fluid accumulation under the pigment epithelium and the retina.

Priorities and Recommendations

- Study further the effects of aging on the anatomy of the neural retina, pigment epithelium, and choroid
- Find out why the maintenance of structural integrity in the central and peripheral retina differ
- Investigate the physiology of retina-pigment epithelial relationships
- Pursue tissue culture studies of the pigment epithelium
- Study the biochemistry of aging effects on retinal and choroidal structure, especially as this relates to the formation of abnormal new blood vessels
- Develop improved methods of studying the choroidal circulation
- Conduct further psychophysical and electrophysiological studies of the normal and diseased macula
- Investigate selective toxic susceptibility of the macula
- Study further the pathology of photoreceptor renewal and phagocytosis
- Identify existing and develop new animal models of macular disease
- Conduct clinical and natural history studies of various types of macular disease
- Perform clinicopathologic correlations in human donor eyes and in eyes from animal models
- Evaluate existing and proposed treatments for various types of macular degeneration

Resource Requirements

The complete list of requirements to support these projects in FY 1978 is presented in the tables at the end of this report. In FY 1977 the NEI will fund approximately $513,000 to support seven research grants and one specialized clinical research center for research in *Macular Diseases*. Additional requirements for FY 1978 are 35 new research grants and two new centers, plus four new research contracts which will bring total funding of this subprogram to approximately $2,096,000.

6

Retinal Detachment

THE RETINA IS COMPOSED of two tissue layers—the neural retina and the pigment epithelium. Any separation of these layers is called retinal detachment. Retinal detachment can and often does cause permanent impairment of vision.

Three factors may cause a retinal detachment: fluid accumulation under the retina (Figure 7); abnormal traction on the retina in the direction of the vitreous cavity (Figure 8); and tears or holes in the retina which permit fluid vitreous to flow into the subretinal space, thereby floating the retina off the pigment

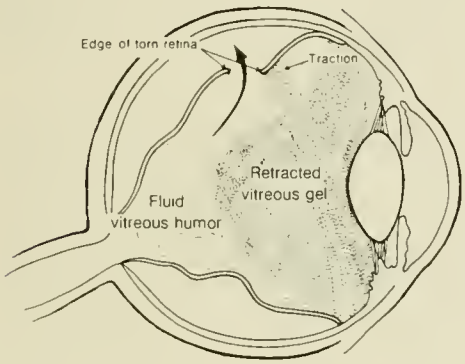

Figure 7. Fluid accumulation under the retina.

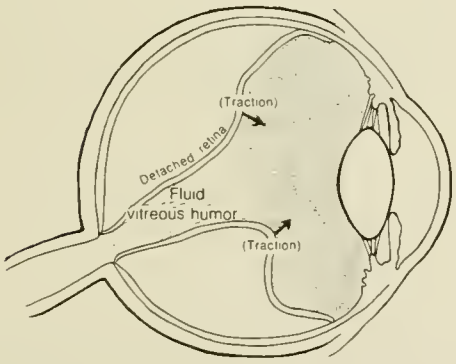

Figure 8. Abnormal traction on the retina.

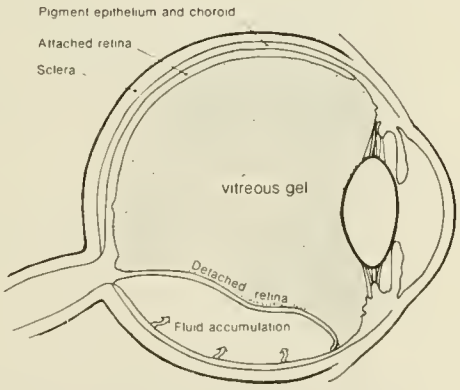

Figure 9. Torn retina.

epithelium (Figure 9). The most frequent type of detachment is one where retinal breaks coexist with a variable amount of vitreous traction.

It is estimated that over 25,000 cases of retinal detachment are diagnosed yearly. In many instances, the untreated disease leads to markedly decreased vision—in fact, to functional loss of the eye. In over 70 percent of cases due to retinal breaks, treatment succeeds in reattaching the retina and restoring at least partial vision.[95] The success rate in the other types is considerably lower.

The overall loss of vision due to retinal detachment is difficult to evaluate. If 25,000 new cases are diagnosed per year, it is probable that each year at least 6,000 people lose most of their useful vision in the affected eye. As many as 15,000 probably recover partial vision as a result of treatment, and 4,000 fully recover their vision following treatment.

Retinal detachment may occur without apparent cause or it may be closely related to other ocular diseases. For instance, retinal detachment often occurs in eyes suffering from known types of degeneration. Perhaps the association of retinal detachment with a high degree of nearsightedness is the most frequent. Importantly, about 2 percent of eyes undergoing cataract surgery will develop a retinal detachment sometime after the operation. Retinal detachment is associated with obvious or latent glaucoma in over 15 percent of cases;[96] and it has a definite relation to developmental defects such as choroidal coloboma, optic pit, congenital retinoschisis, and facial deformities. Retinal detachment sometimes is related to metabolic diseases such as Marfan's syndrome and Ehlers-Danlos syndrome, and it may occur as a complication of diabetic retinopathy, retrolental fibroplasia, uveitis (especially peripheral uveitis), and tumors of the choroid and retina. Retinal detachment follows ocular trauma in about 16 percent of cases.[97]

The diversity of relationships appears disconcerting. In fact, the pathogenesis of retinal detachment in all these cases is determined by a limited number of factors: traction exerted on the retina in the direction of the vitreous, weakening of the normal chorioretinal adhesion, and localized atrophy of the retina which leads to the development of retinal breaks.

Accomplishments

In the past 25 years, considerable progress has been made in the diagnosis and treatment of retinal detachment. Many of the advances made were supported by the National Institutes of Health, most recently by the National Eye Institute. The accuracy of retinal detachment diagnosis has improved considerably with the introduction of new and improved techniques such as binocular stereoscopic ophthalmoscopy with scleral depression.

Thanks to such diagnostic techniques, treatment has also become more effective. Results of treatment have been further improved by the development of scleral buckling operations that reestablish the anatomical position of the retina. Refinements in diathermy, cryosurgery, and photocoagulation have led to more effective ways of producing a chorioretinal adhesion for sealing the retinal breaks.

Progress in all these areas has improved the reattachment rate of retinal detachment caused by retinal breaks from below 40 percent in 1947 to over 70 percent today.[95] It has also made possible a decreased hospital stay from an average of four weeks to one week.

There are at present seven research projects supported by the National Eye Institute directly relating to retinal detachment, although only two are totally directed toward the study of this disease. The total amount spent yearly on these seven projects is approximately $690,000. Four of the projects exclusively

concern diagnosis; two deal with methods of treatment; and one covers both areas. A small portion of one program is devoted to the study of pathogenesis of retinal detachment.

Research Objectives

- Improve techniques for diagnosis of retinal detachment
- Elucidate the pathogenesis of the disease
- Develop improved treatment methods
- Find ways of preventing retinal detachment
- Develop animal models of human retinal detachment

Research Needs and Approaches

Diagnostic Techniques

By continuing and expanding existing research efforts, the diagnosis of retinal detachment could be improved substantially. Major opportunities and needs exist in optics and in electrical and functional testing of the retina.

Optics

Optical methods are essential for diagnosing retinal detachment. The ophthalmologist looks for breaks in the retina with an ophthalmoscope or a slit lamp. Research to improve these techniques must include continued study of the optical model of the human eye. This, in turn, will permit the development of instruments to see the vitreous body and the various retinal layers with greater clarity. Further attempts should be made to enhance the definition of fundus images by computer techniques. Other research needs include:

- Development of ways to measure local retinal thickness and lines of stress.
- Development of wide-angle ophthalmoscopy and photography and in depth investigation of its potential in clinical practice.
- Study of narrow band, monochromatic light, especially its possible use to improve the definition of specific fundus structures, and detailed study by reflectometry and fluorophotometry of various points in the fundus. Such studies should lead to an improved diagnosis of the earliest changes in disease.
- Study of specular reflections for the examination of the retina. Specular microscopy is a technique by which the interface between membranes reveals structural details that are otherwise invisible.
- Study of holography of the eye to determine whether or not this unique method can give detailed information on the retina and choroid.

Research in optics should lead to improved ophthalmoscopic and photographic images of the fundus under various conditions and also to improved projection of images onto the fundus, so as to improve the accuracy of aiming extremely fine

photocoagulation beams. In particular, studies in this area should provide the following benefits:

- Measurement of local retinal thickness and of lines of stress will provide early warning signals of retinal holes and tears.
- Wide-angle ophthalmoscopy and photography will improve diagnosis and follow-up of extensive lesions (such as retinal detachment, diabetic retinopathy, uveitis, tumors, and trauma). It will reduce costs, save time, and increase accuracy. It will replace the current practice of making montages of fundus photographs for extensive lesions or of sketching such lesions by hand.
- Detailed study of the fundus with narrow band monochromatic light will supply immensely useful details of the structure of the various layers of the retina. It could well lead to earlier diagnosis in several pathological conditions and it could also lead to the discovery of heretofore unsuspected lesions.
- Fundus reflectometry—the measurement of light reflected from the back of the eye—will permit accurate evaluation of the circulation in the optic disc and macular area. This, in turn, will provide new tools to probe the cause and consequences of certain diseases of the disc (especially glaucoma) and macula. Such techniques may not only lead to reliable means of measuring blood flow but also of oxygen consumption in discrete areas of the retina and choroid. Such evaluation should help substantially in predicting the development of retinal detachment and of other retinochoroidal diseases. It could also be invaluable in improving the prevention of retrolental fibroplasia (see Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*).
- The study of specular reflections may make it possible to study interfaces such as the outer surface of the vitreous cortex, the inner and outer limiting membrane, and perhaps the inner surface of the pigment epithelium. In addition, it would permit detailed study of the pathological interfaces. Such information would enhance understanding of the development of fundus diseases, as in the early stages of retinal detachment, or in vascular and degenerative conditions.
- The practical application of holography to the eye could replace the optical methods now used to examine not only the retina but the transparent media as well.

Electrical and Functional Testing of the Retina

Before attempting to treat the diseased retina, it is important to determine its potential for recovery. This can be done by electrical and functional studies.

Three electrical techniques are available: electroretinography (ERG), visually evoked response (VER), and electro-oculography (EOG). These and similar techniques should be further developed in order to improve their use for accurate determination of the location and degree of retinal impairment. Specifically, further research should be performed in focal ERG and VER for delineating the functional potential of specific areas of the retina. Particularly important is the development of techniques to determine the potential for recovery of the macular region. A recently developed test of electrically evoked response in the retina (EER) should be developed further to evaluate minimal function of the ganglion cells and optic nerve in severe cases of retinal detachment.[98]

Functional testing of the retina is done by psychophysical procedures. Simple, accurate, and easily repeatable techniques are needed that will help establish the

degree of functional impairment of both the detached and the reattached retina, plus the potential for further visual recovery. The development of accurate, automated procedures for mapping the visual field and recording other functional measurements should be encouraged. These techniques may involve the use of an eye-tracker to stabilize fixation and of a computer to evaluate and map the results.

Functional tests that would permit more accurate measurement of retinal damage and the potential for recovery are very important, not only in cases of retinal detachment but also in many instances of macular disease. The continued development of the recently devised grating tests should be encouraged.[99]

Studies which have potential for improving diagnosis of retinal detachment are:

- Electrical testing which could help improve substantially the ability to diagnose, establish a prognosis, and monitor the course of retinal detachment and of therapeutic reattachment.
- Functional testing of visual performance which can help in a similar way. A combination of both techniques will, it is hoped, help in predicting the development of retinal detachment. (See report of the *Sensory and Motor Disorders of Vision* Panel, Chapter 3, *Optical and Pupillary Disorders.*)

Research in Pathogenesis

This is where the greatest research effort should be made. Three areas of investigation appear to be promising: retinochoroidal adhesion, vitreoretinal relationships, and study of the blood-retina barrier.

Retinochoroidal Adhesion

For a long time, no positive attachment of the retina to the underlying pigment epithelium was recognized. Today, two types of attachment are thought to exist: one is due to a visco-elastic force produced by a thin layer of glucosaminoglycan;[100] the other, much stronger, exists only in life and its nature is still uncertain.[101] In 1975, it was found that the pigment epithelial cell processes which surround the outer part of the rods and cones contain an orderly array of fine, muscle-like filaments.[102] These filaments may play an important role in retinochoroidal adhesion. In order to understand the nature of retinal adhesion, much more knowledge of the interaction between pigment epithelial processes and the neural retina is necessary. Such studies are essential to understanding the pathogenesis of retinal detachment.

In addition, the chorioretinal adhesion produced by diathermy, cryoapplication, or photocoagulation should be fully investigated. Specifically, a comparison of the binding strength resulting from application of the above treatments would be of value.

It is hoped that detailed knowledge in this area will provide the key to medical prevention. The present working hypothesis is that retinal adhesion weakens well before retinal detachment occurs.

Vitreoretinal Relationships

Normally, the outer part of the vitreous cortex is in contact with the retina's inner limiting membrane. The interaction between these two layers is poorly

understood, and as a result, it is not known whether vitreous detachment produces functional changes in the retina. A detailed anatomic and biochemical study of this problem is long overdue.

Why or how vitreous shrinkage occurs is also largely unknown. A study of the pathogenesis of extensive shrinkage of the vitreous base, which leads to many severe cases of retinal detachment, is particularly important.

The cause of abnormal vitreoretinal adhesions, which precede vitreous shrinkage and produce retinal tears, needs to be investigated both in animal models and in humans.

Preretinal membranes—membranes which lie at the surface of the retina—are a most important area of investigation. The nature (type of cells and biochemical composition of acellular elements) of preretinal membranes needs to be determined. It must be learned not only what causes the growth of such membranes but, if effective therapy is to be developed, how this growth can be controlled.

Detailed knowledge of these relationships may make it possible to prevent preretinal scarring, the basic cause of most incurable retinal detachments.

Study of Blood-Retina Barrier

There are indications that in all cases of retinal detachment the subretinal fluid contains certain blood elements. In cases without retinal breaks, the subretinal fluid may originate entirely from the bloodstream. Since such fluid collection plays a role in retinal detachment, a careful study of the blood-retina barrier and of the factors which control this barrier seems essential.

In retinal detachment secondary to such disorders as uveal effusion, the cause of fluid collection is unknown.[103] Research on the origin (retinal or choroidal) and composition of this fluid may give new insights into the pathogenesis of types of retinal detachment which are presently incurable.

Disturbances in the blood-retina barrier are probably the main underlying cause of retinal breaks and of all exudative or transudative retinal detachments. Increased knowledge in this area could lead to a more rational means of preventing retinal breaks and of subretinal exudation or transudation (see also Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities,* for additional discussion of the importance of blood-brain barriers).

Treatment Methods

Studies of surgically induced chorioretinal scars need to be undertaken to determine the adhesive power of the various types of scars. Recent work indicates that, in many cases, a chorioretinal scar may not be necessary to bring about reattachment of the retina.[104] Release of subretinal fluid with scleral buckling (without induced scarring) may be all that is needed in most cases.

Better scleral implants need to be devised. Two categories are desirable: nonabsorbable soft implants without air space and with a very smooth surface, and absorbable implants without antigenicity. Both types should be infection-resistant.

Treatment of severe rhegmatogenous retinal detachment—resulting from giant retinal tears with massive preretinal retraction or due to optic pits or choroidal coloboma—needs considerable improvement. Better knowledge of pathogenesis should facilitate development in this area.

Improvements in surgical techniques for reattachment of the retina will depend largely on improvements in vitreous surgery, either with or without tissue removal (see Chapter 9, *Vitreous Humor*).

The potential benefits from research on treatment methods include the following:

- Research on the adhesive power of induced chorioretinal scars will lead to more rational use of diathermy, cryoapplication, and photocoagulation. It will also direct further efforts to refine these methods.
- Better scleral implants will lead to safer and more effective techniques of scleral buckling.
- Improved techniques of treating severe cases of retinal detachment are needed to improve the rate of reattachment and visual restoration in presently incurable cases.
- Improvements in vitreous surgery should permit successful reattachment of the retinas of many more patients.

Research on Prevention

Until now, prevention of retinal detachment has consisted of treating retinal breaks before a retinal detachment develops. However, many retinal breaks never lead to retinal detachment. A ten-year survey made on a stable population (Israel) indicates that the introduction of prophylactic retinal surgery has not decreased the incidence of retinal detachment.[105] Clinical study of this question should seek to identify:

- The most suitable cases for prophylactic treatment. Methods for diagnosing cases likely to progress toward retinal detachment are lacking. A carefully designed prospective study should be carried out to characterize those cases most likely to benefit from treatment.
- The best method of prophylactic treatment. Should it consist of an induced chorioretinal scar or of a buckle, or of both?
- The biochemical and anatomical factors that predispose to retinal detachment cases of myopia, lattice-like degeneration, and acquired retinoschisis; certain developmental eye and systemic anomalies; some inherited eye diseases (such as Wagner's disease or congenital retinoschisis); and inherited systemic diseases such as Marfan's syndrome.
- The relationship between intraocular blood circulation and retinal detachment. Retinal and choroidal circulatory deficiency may be a common denominator in many cases of retinal detachment. Whether such deficiency is a cause of retinal detachment or the result of another undiscovered factor is not known. Methods to measure regional circulatory defects in the living eye should be developed further (see Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities)* and be used in a prospective study of eyes which are thought to be at risk to developing rhegmatogenous retinal detachment.

Potential benefits to be realized from research on prevention include:

- Better selection of cases for surgical prophylactic treatment which will avoid many unnecessary operations and, where appropriate, lead to more effective prevention of retinal detachment.

- Better knowledge of predisposing factors which is necessary for effective medical prevention of retinal detachment.
- Improved knowledge of the influence of circulatory deficiencies which is also necessary for effective prevention, either medical or surgical.

Development of Animal Models

Animals known to be predisposed to retinal detachment (such as those with an elongated eyeball) should be acquired and bred. Retinal detachments that can be produced by noninvasive manipulations should be developed. There is no way to overstate the value of animal models in retinal detachment research or the present need for them. The isolated mammalian eye perfused with whole blood is useful for study of circulatory changes in the retina and choroid, research on the influence of drugs on those tissues, microscopic observation in situ of changes brought about by chemical or traumatic manipulation of the choroid and retina, and measurements of ERG and optic nerve response after artificially induced retinal detachment or other manipulations.

Much of the research described in the preceding section cannot be adequately carried out without animal models. Were they available, the means would be at hand to perfect treatments that would save the vision of many persons.

Priorities and Recommendations

The following recommendations are based on several criteria: expected return in terms of cost and effort, potential for immediate benefit to patients, long-term value in terms of possible sight prevention, and chance of successful completion.

- Conduct research in new diagnostic techniques including optics and electrical and functional testing of the retina
- Investigate vitreoretinal osmotic relationships
- Increase understanding of retinochoroidal relationships and the blood-retina barrier
- Compare the maintenance of structural integrity in the macula and periphery
- Investigate means of preventing retinal detachment
- Develop animal models of the disease
- Evaluate current and new methods of treatment

Resource Requirements

The funding needs for carrying out each of the above recommendations are estimated in the tables at the end of this report. In FY 1977 the NEI will support only two research grants for investigating *Retinal Detachment*. Additional requirements for FY 1978 include 20 new research grants, three specialized clinical research centers, and two research contracts. With these increases, the total NEI funding of this subprogram in FY 1978 will be an estimated $4,216,000.

It must be recognized that a certain degree of overlap exists among the various subprograms in *Retinal and Choroidal Diseases* and, hence, in their manpower

requirements. For example, study of diagnostic techniques in retinal detachment is relevant to diagnosis of practically all diseases of the retina, choroid, and vitreous; research on electrical and functional testing of the retina will no doubt have an impact on diseases of the pigment epithelium, myopia, and diseases of the choroid; study of vitreoretinal relationships will have a potential impact on research on the vitreous; investigation of the blood-retina barrier is also important for vascular and circulatory abnormalities; study of factors which predispose to retinal detachment is relevant to developmental, hereditary, and degenerative diseases; research on the influence of circulatory deficiencies in this subprogram will have an impact on vascular and circulatory abnormalities; and the development of animal models is important to nearly the whole field of chorioretinal diseases (see appropriate chapters for related discussion). These overlaps have been considered in evaluating the needs for additional projects and manpower.

7

Inflammatory Disorders

INFLAMMATORY DISORDERS of the retina and choroid comprise a large group of highly destructive diseases: they are frequently blinding and in certain cases painful. Characterized by the accumulation of inflammatory cells and fluid (edema), these diseases commonly affect not only the retina and choroid but also the vitreous body and the front of the uvea (the ciliary body and iris). When the iris and ciliary body are involved, secondary glaucoma and "complicated" cataract may result. Although these disorders are commonly referred to as "uveitis," it should be stressed that parts of the eye other than the uvea are frequently involved.

Inflammatory diseases of the retina and uvea can be subdivided into two major categories: infectious and noninfectious. Among the causes of the former are bacterial infections such as syphilis, viral diseases such as cytomegalovirus

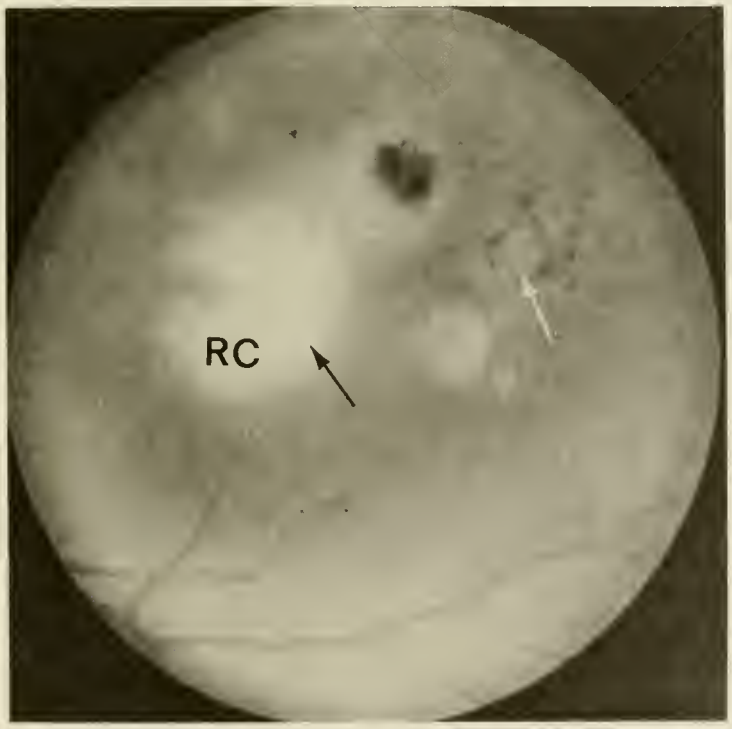

Figure 10. Appearance of the fundus in recurrent ocular toxoplasmosis.

retinitis and herpes infections, fungal infections such as histoplasmosis, and parasitic infestations such as toxoplasmosis and toxocariasis. In Figure 10, a fundus photograph of a case of recurrent ocular toxoplasmosis, the black arrow indicates an acute retinochoroditic lesion; the white arrow, a retinal scar.

Other inflammatory diseases are believed to arise from immunologic insults. These include lens-induced uveitis, sympathetic ophthalmia, and retinal vasculitis. The first of these is believed to be an allergic reaction of the uvea to the patient's own lens; the second, a hypersensitivity to proteins present in the outer retina and uvea; and the third, an inflammatory reaction to deposits of antigens and antibodies in the retinal vessels.

As a whole, such diseases come under the broad category of hypersensitivity phenomena. Although they may be initiated by trauma or by infection, they are self-sustaining for they continue to plague the patient long after the trauma has been repaired or all traces of the original infection have disappeared. These processes are believed to represent autoimmune phenomena—disease processes in which the body's immunologic defense system is turned against its own tissues. Melanin-containing cells in particular seem to be the special targets of autoimmune processes, but the reasons for this are not clear. It has been postulated that trauma or infection changes the chemistry of these normal tissues in such a way that they become autoantigenic. The immunologic surveillance system of the body regards them as "nonself" and attacks them.

The so-called "collagen diseases," typified by rheumatoid arthritis and lupus erythematosus, are also believed to represent autoimmune phenomena. In the eye, these diseases attack the sclera and uvea (rheumatoid arthritis) and the retinal vasculature (lupus erythematosus), but the relationship of the ocular lesions to the systemic diseases is as yet undetermined.

In addition to these two categories of inflammatory disorders—infectious and noninfectious—a third exists. This category includes sarcoidosis and Behçet's disease, diseases which are suspected to be infectious in origin, but have thus far evaded certain etiologic diagnosis.

The principal causes of blindness from inflammatory diseases of the retina and choroid are destruction of photoreceptors in the macula, damage to the nerve fibers that transmit visual impulses to the optic nerve, and opacification of the vitreous overlying the inflammatory lesions.

It is estimated that in 1972 approximately 67,000 Americans had severe visual impairment from uveitis; of these, 23,000 were legally blind.[1] In the same year, an estimated $10 million was spent for medical care of such patients.

These figures probably represent only the tip of the iceberg as far as ocular disability from inflammatory disorders is concerned. Many patients with uveitis suffer pain and increased sensitivity to light, see floating spots, and have some degree of visual impairment for months or years. These complaints do not come to the attention of agencies which collect data on visual disabilities. The real tragedy is that, in the absence of severe pain, inflammatory disease of one eye may be neglected until the second eye becomes affected. Visual acuity examinations by school nurses or by driver's license authorities help bring such individuals to the attention of ophthalmologists, but a surprising number of patients slip through such screening unnoticed. Thus, it is probable that the magnitude of the problem of inflammation of the retina and choroid is greater than any collection of prevalence data would show.

Accomplishments

Through basic and clinical research, extraordinary advances have been made in the diagnosis and treatment of inflammatory diseases of the retina and choroid.

Diagnosis

For many years, guesswork prevailed in the diagnosis of chorioretinal inflammations, and treatment was all too often instituted on the basis of these guesses alone. In the first half of this century when pulmonary tuberculosis was widespread among our population, inflammatory disease of the choroid and retina was most often attributed to tuberculosis. Subsequent careful histopathologic examination of eyes disclosed that the true pathogen was the parasite *Toxoplasma gondii*[106] or some other infectious agent. In some cases, it was possible to isolate the offending pathogens by injecting the minced soft tissues removed from these eyes into test animals such as mice. The results of these procedures provided invaluable diagnostic information for other patients with similar fundus lesions.

For the most part, information concerning the probable cause of a patient's inflammatory disease has been obtained only by indirect means. Blood tests, skin tests, and X-rays comprise the bulk of this information, but these tests only provide evidence of the systemic diseases to which the patient has been exposed. If two or more different serologic tests are found to be positive, the examiner is still uncertain of the most likely cause of the patient's ocular inflammatory disease.

Recently, a number of direct approaches to the diagnosis of the diseased eye have been developed. Removal of a small sample of aqueous humor through a puncture in the peripheral cornea (keratocentesis) has permitted the isolation and identification of bacteria in some cases[107] and the demonstration of specific antibodies in others.[108] Armed with such data, ophthalmologists have been able to employ specific antimicrobial therapy which has permanently cured certain of these cases. In other cases, where studies of aspirated aqueous humor failed to provide the answer, diagnostic sampling of the vitreous humor has produced a definitive diagnosis, particularly in cases of bacterial and fungal endophthalmitis.[109,110]

Other important advances include the development of methods for visualizing the vascular pathways of the retina and choroid. Such dyes as fluorescein and indocyanine green, injected intravenously, reveal the details of blood flow through the retinal and, to some extent, the choroidal vessels when viewed with light of specified wavelengths. In the case of fluorescein, leakage of this dye through the endothelium of damaged retinal blood vessels indicates localized inflammation or, in some cases, the presence of neovascularization. If inflammation has caused damage to the retinal pigment epithelium, the fluorescein that normally diffuses out of the choroidal vessels may pool in or under the sensory retina in the late phases of fluorescein angiography. The degree to which fluorescein diffuses into the optic nerve head and submacular choroid may indicate the severity of inflammation, and this can now be quantitated by a noninvasive technique known as fundus reflectometry.[111]

Treatment

New and more efficacious forms of therapy have been developed for such diseases as ocular toxoplasmosis and *Candida* endophthalmitis, largely through the aid of animal models of these diseases. Thus, experimental toxoplasmosis in the rabbit eye has been effectively cured with intramuscular and periocular injections of clindamycin, a newly discovered derivative of lincomycin.[112] *Candida* endophthalmitis has been cured with 5-fluorocytosine, a drug much less toxic than the standardly used amphotericin B.[113] The removal of severely

inflamed vitreous by one of several currently available vitrectomy techniques is responsible for the restoration of useful vision to a number of patients suffering from endophthalmitis.[114]

The dangers of infectious diseases due to facultative pathogens (ones that take advantage of a weakened host) in patients receiving excessive amounts of corticosteroids or other immunosuppressive agents have been brought to light.[115] This information, which first came to the attention of ophthalmologists through the observations of immunosuppressed patients[116] (e.g. lymphoma victims or organ-transplant patients), has also been confirmed in animal models. Under conditions of immunosuppression, organisms normally held at bay by the immunologic defense system are free to proliferate in an unchecked manner.

Where, on the other hand, the immune mechanisms play a principal role in a disease process, immunosuppressive agents have proved to be of great value. Such autoimmune diseases as sympathetic ophthalmia, rheumatoid sclero-uveitis, and Behçet's disease have been treated very satisfactorily with cytotoxic agents such as chlorambucil after all hope had been abandoned for success with conventional therapy. It is likely that a significant therapeutic effect is accomplished through the induction of immune tolerance.

Research Objectives

- Discover the cause or causes of inflammatory diseases of the retina and choroid
- Improve the diagnosis and treatment of these disorders

Research Needs and Approaches

Improved Diagnosis: The Recognition of the Pathogen

Because the precise etiology of the majority of uveitis cases remains unknown, increased effort must be directed toward developing methods for making a direct diagnosis from ocular tissues. For endophthalmitis of infectious origin, it should be possible to make an etiologic diagnosis by direct sampling of the vitreous humor. An important beginning has been made: it is now possible to aspirate vitreous through a hypodermic needle inserted into the globe at the pars plana. By this means the offending organism can often be identified in the vitreous in cases where the aqueous humor has proved to be sterile.[117] Although the potential dangers of this technique include the introduction of exogenous infectious material into the eye, the inadvertent production of retinal detachment, and the possible seeding of infectious material along the needle track upon withdrawal of the instrument, in practice the incidence of such complications has been low. Since the potential rewards are high, more extensive use of this technique in the future seems justified. This is an area of applied research where the immediate reward is improved ability to institute appropriate therapy quickly. Often such therapy involves the use of toxic drugs that are administered intravitreally or intravenously. Their use can be justified only if a precise etiologic diagnosis has been made beforehand.

Other types of important information can also be obtained by this procedure. For instance, finding eosinophils in the vitreous aspirate might suggest the presence of a parasitic infection, or finding cells with large hyperchromatic nuclei

and prominent nucleoli would indicate that a malignant tumor was masquerading as an inflammation. Each condition would have to be treated entirely differently from bacterial or fungal endophthalmitis. Once again, the trauma and potential risks of vitreous aspiration seem justified by the value of the information gained.

The development of surgical techniques for whole eye-wall resection in the treatment of malignant melanoma may make chorioretinal biopsy possible. Chorioretinal biopsy can also be done through a transvitreal approach.[118] The opportunity for direct histopathologic examination of affected tissues will solve many diagnostic problems, particularly those concerned with distinguishing inflammatory lesions from degenerative conditions. Here again, much needless and potentially dangerous therapy might be avoided if an accurate diagnosis could be made. At the same time, the risks of performing a chorioretinal biopsy on a well-encapsulated, unsuspected tumor are fully appreciated. Potential benefits must always be weighed against known risks.

Clinicopathologic Studies

The need for definitive clinicopathologic studies is evident. Pioneer histopathologic studies of the eyes of patients that have been examined and photographed during life have already provided important clues to the origin and pathogenesis of chorioretinal inflammations. Such work is, however, still in its infancy. Isolation of infectious pathogens from the minced tissues of enucleated eyes has been accomplished in only a small number of cases. A concerted effort must be made to form a registry of well-studied uveitis patients. Eyes enucleated at the time of death or at some time prior to death would be fixed under optimal conditions and carefully studied. Institutions capable of performing reliable light and electron microscopic studies of enucleated uveitis eyes should be given funds for additional studies of this type, and collaborative studies should be encouraged wherever they are deemed feasible (see Chapter 12, *Special Areas of Future Interest*, for greater detail).

Animal Models

The development of animal models of inflammatory eye diseases should also be encouraged. Where important clues to the nature of a given inflammatory disease have been discovered, they should be followed up by attempts to produce similar disease in the eyes of laboratory animals. Such studies are necessary both to determine the natural course of a disease and to discover the effects that various forms of drug therapy might have on it. This is particularly true of many immunologic disorders whose pathogenesis is far from completely understood. In the infectious forms of uveitis, the development of efficient antimicrobial therapy is absolutely dependent upon such models, yet few have been developed. In this connection, animals with eyes similar to those of man should be selected wherever this is economically feasible. Although many past studies have been performed on the rabbit, this animal, because of its peculiarly avascular fundus, is not the most appropriate experimental subject for many studies.

Evaluation of Treatment

Controlled, randomized trials of drug therapy should be attempted in situations where promising leads have been supplied by animal experiments and where preliminary trials on humans indicate that the drug is both safe and

efficacious. Meticulous attention should be given the design of double-masked evaluations of such drugs, eliminating where possible both patient and physician bias. The numbers and types of human subjects should be selected to provide adequate controls and incontestable statistical evaluation. Few drugs currently in use for the treatment of inflammatory diseases of the retina and choroid have been subjected to such testing.

Priorities and Recommendations

- Improve methods of tissue diagnosis, including direct sampling of the vitreous as a diagnostic technique, and develop methods for chorioretinal biopsy.
- Correlate carefully documented clinical findings in life with histopathologic findings in eyes obtained at death. To make this effort effective, a specialized registry is required.
- Investigate the experimental induction and treatment of inflammatory eye diseases in animals.
- Investigate the role of immunity in ocular inflammation especially in systemic collagen diseases and in diseases affecting melanin-containing cells.
- Utilize tissue culture of the retina to investigate inflammatory diseases.
- Conduct controlled, randomized trials of various treatment regimens to select those that are most effective.

Resource Requirements

To implement the programs suggested above, significant increments in both research funding and manpower must be added to the presently available resources. In support of research on inflammatory disorders of the retina and choroid, the National Eye Institute will fund approximately 14 extramural grants in FY 1977 for an estimated total cost of $943,000.

The important leads that have already been obtained in the field of inflammatory diseases of the retina and choroid justify the funding of at least 18 more research grants in FY 1978 including the support of clinical trials. (See detailed list of recommendations at the end of this report.) To implement these projects, additional men and women must be trained in the highly sophisticated fields of immunology and microbiology, especially as they are applied to the eye. Training obtained through the traditional mechanism of NEI's Special Fellowship Program is considered a good method of accomplishing this goal. The training period should be at least two years, and preferably three years, in duration. Alternatively, attempts to recruit researchers in other fields who have received appropriate training should also be undertaken. Such recruitment, if successful, would bring to eye research talented, skilled individuals, thus saving both time and money. In situations where controlled clinical trials are envisioned, training in centers with proven capabilities in clinical research methods should be stressed. This training should include methods for implementing randomized, double-masked trials, the principles for applying appropriate statistical methods, and use of the proper tools for ultimate analysis of therapeutic results. The Panel

also recommends two additional specialized clinical research centers and one research contract in *Inflammatory Disorders* for FY 1978, bringing total funding of this subprogram to $3,173,000 in that year.

8

Uveal Tract

THE UVEAL TRACT, the middle coat of the eye, is sandwiched between the tough, white outer scleral coat and the retina (see Figure 11). In the back part of the eye, the uveal tract is represented by the choroid, a rich vascular network supplying nutrients to the retina. Separating the capillary network of the choroid—the choriocapillaris—from the retina is a thin, elastic sheet called the Bruch's membrane.

The most forward part of the uveal tract is the iris, the delicate, colored, movable diaphragm that regulates the amount of light allowed to strike the retina. Just behind the iris, between it and the choroid, is the ciliary body. This structure is composed of secretory cells, which produce the aqueous humor, and the ciliary muscle, which controls accommodation of the lens. Accommodation of the lens permits the focusing on the retina of images of objects at various distances. Loss of accommodative ability with aging necessitates the use of reading glasses. The choroid, ciliary body, and iris taken together comprise the uveal tract.

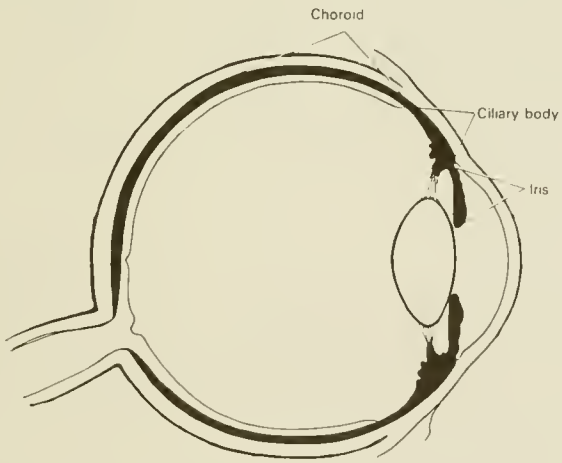

Figure 11. Diagram of the uveal tract.

The uveal tract plays an important supporting role for many of the structures of the eye. Unfortunately, it is often at risk. Numerous ocular diseases result primarily from malfunction of the uveal tract: circulatory disorders, inflammations (uveitis), and macular degeneration are the most common and have been

discussed at length in previous chapters of this report. It should be noted, however, that the posterior part of the uveal tract appears to be singularly vulnerable to debilitating changes associated with aging. Some degree of sclerosis in choroidal vessels is observed in 50 percent of the population over age 60. In a small but tragic minority, abnormal vascular channels that breach Bruch's membrane and contact the retinal pigment epithelium are seen.[119] Sclerotic changes in Bruch's membrane and the formation of neovascular channels exert deleterious effects on retinal (especially macular) function (for details, see Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*, and Chapter 5, *Macular Diseases*).

In this chapter, some of the basic anatomical and physiological aspects of the choroid, Bruch's membrane, the iris, and the ciliary body are considered. This chapter also discusses how advances in knowledge of these structures have contributed to the clinical recognition, understanding, or treatment of certain uveal diseases and how the lack of crucial information hampers progress against other uveal disorders.

Accomplishments

Significant research advances have been made in recent years toward understanding the development, structure, function, and pathology of the uveal tract. These have followed detailed studies of each uveal tract component and have drawn on important technical advances, such as electron microscopy and angiography with fluorescent dyes.

The Choroid

It is now known that the choroid consists of a rich vascular network with associated nerves and intervening connective tissue. Of primary importance to ocular pathology is the structure of the choroidal vasculature. Its capillary network, called the choriocapillaris, is responsible for nourishing the entire thickness of the retina in the central foveal region and the outer retinal layers in the rest of the eye. The choroidal capillary network is singularly prone to several hazards: it traps foreign material, it gives rise to new blood vessels, and it is subject to debilitating changes with age. Particularly, the choroid is a prime target in the body for inflammations and for metastatic tumors (see Chapter 4, *Tumors*).

In spite of the fundamental importance of the choroidal vascular system, it has not been possible to visualize it in the clinical examination because the melanin pigment of the overlying pigment epithelium acts as an effective optical barrier. Spurred on by the development of precise means to photograph the more superficially placed retinal circulation, scientists are now in an advanced stage of developing an analogous method by which the more deeply placed choroidal blood vessels can also be seen.

In essence, the method depends on the selection of longer wavelengths of light which can pass through the pigment barrier unimpeded. To accomplish this, a harmless fluorescent dye is injected into the bloodstream. When the dye reaches the eye, it is stimulated by red light beams and fluoresces. The choroidal blood vessels light up in sharp relief. They are photographed and permanent records are obtained for clinical evaluation. This outstanding development is just beginning to increase understanding of choroidal vascular anatomy in health and disease.[33]

Bruch's Membrane

Bruch's membrane—a thin, elastic sheet separating the choroid from the pigment epithelium—is really a two-layered structure. It is composed of the basement lamina derived from the pigmented retina and a layer of collagen and elastic fibrils contributed by the choroid. Bruch's membrane acts as a separator, a sieve, and as a support. As a separator it provides an intact barrier between the retina and choroid, the importance of which is underscored by the havoc wreaked by its failure. There are a number of visually disabling diseases in which abnormal blood vessels transgress Bruch's membrane and lodge under the retinal pigment epithelium. Through transudation, hemorrhage, local growth, and fibrous metaplasia, these vascular growths exert markedly deleterious effects on retinal (especially macular) function.[88]

Even while acting as a separator, Bruch's membrane must also act as a loosely knit molecular sieve, for it is important that molecules up to a considerable size pass through it so that the retina can be nourished and so that waste products can be carried away. Further, the toughness and durability of Bruch's membrane let it absorb to some degree rapid pressure changes within the eye.

Lastly, Bruch's membrane acts as a support—on one side, it forms an integral part of the finest radicles of the choroidal circulation; the tightly packed pigment epithelium is seated directly upon its other side.

The Iris

The iris functions as a movable diaphragm. The diameter of the pupillary opening is controlled by two sets of muscles: the sphincter that closes the pupil and the dilator that opens it. Thanks to numerous anatomical studies, the detailed ultrastructure of the iris is now known. How the complementary muscles of the iris are controlled by the autonomic nervous system is also known. As a result of related pharmacological studies, safe and reversible dilation of the pupil with drugs is possible, a capability invaluable in clinical examination, treatment of inflammations, and surgery of the anterior segment.

It is also known that the iris normally permits the aqueous humor to flow from the posterior chamber to the anterior chamber. This is an essential function. As detailed in Chapter 7, *Inflammatory Disorders,* and in the *Glaucoma* Panel report, when the flow of aqueous is blocked, the intraocular pressure may rise drastically to a level so high that it endangers sight.

The Ciliary Body

The ciliary body has two essential functions: it produces the aqueous humor, and it participates in accommodation of the lens.

Aqueous humor is formed as blood fluids leave the capillaries of the ciliary body, traverse the ciliary epithelia where some substances are added and others removed, and finally enter the posterior chamber. In this process, the ciliary epithelium acts as a barrier or tissue screen to prevent entry of noxious or undesired constituents of blood plasma, at the same time secreting the complex solution called the aqueous humor. The importance of the normal functioning of this system cannot be too strongly emphasized, since the aqueous humor brings essential nourishment to the lens and cornea and carries waste products away. As evidence of the importance of barrier function, there is a recent report that

abnormal intraocular penetration of phospholipids can lead to cataract formation.[120] Under normal conditions, the carefully controlled secretion of aqueous humor also maintains the intraocular pressure at an even level.

Research Objectives

- Learn more about the development, structure, and function of the uvea, with special emphasis on osmotic, vascular, and immunological relationships
- Understand the nature of diseases of the uveal tract, especially conditions that affect macular vision

Research Needs and Approaches

Anatomy

In certain types of retinal degenerative diseases, the region of the choroid underlying the macular retina is predisposed to damage. The reason for this is not known. Anatomical studies should attempt to find differences between the peripheral and central choroid and to explain the nature of these differences.

It is known that blood vessel changes affecting the macula occur primarily with aging. Particular attention should be focused on changes in the small choroidal blood vessels and in their environment during the aging process.

Bruch's membrane appears to be particularly susceptible to aging changes.[88,119] Anatomical abnormalities such as breaks in and calcification of Bruch's membrane merit expanded investigation.

Physiology

The choroidal blood flow is responsible in large part for the nutrition of the retina. It is not yet clear what controls the extent and location of flow to these vessels.[121] However, it is recognized that alterations in choroidal blood flow can have serious consequences for retinal function. Therefore, the normal mechanism for control of this flow as well as changes that occur from elevated intraocular pressure or from systemic hypertension must be investigated.[88]

The accurate measurement of blood flow in the choroid and choriocapillaris is now under study with a technique called fundus reflectometry.[111] Without these important studies of choroidal hemodynamics, there would be little understanding of what constitutes a pathological change in flow to the choroid, and it would not be possible to diagnose derangements of that flow accurately.

In a variety of pathological instances, fluid accumulates on one or another tissue level between the choroid and retina. Therapy is stymied by incomplete understanding of the normal movement of water between the vitreous, retina, and choroid. Preliminary information indicates the existence of large osmotic gradients from retina to choroid.[122] A substantial effort to define how these gradients arise and are maintained is warranted because this will build the groundwork for understanding how they can go awry.

Biochemistry

It is now possible to maintain tissues taken from the eye in artificial

circumstances, either to study the metabolic requirements of normal tissue or the biochemical abnormalities of disordered tissue. Such tissue and organ culture techniques should be pursued in the study of diseases of the choroid.

New vessel growth from the choriocapillaris and from the iris vessels probably represents a response to an angiogenic stimulus. One such stimulus, known as tumor angiogenesis factor, has recently been isolated from solid tumors.[93] Similar substances should be sought from eyes with choroidal or iris neovascularization. Such a discovery would have particular clinical importance since an inhibitor of angiogenesis has also been found.[123]

Pathology

Clinicopathologic correlations in diseased tissues from a clinically well-studied eye obtained at autopsy often provide invaluable information. For example, for many years the cause of a particular type of ocular inflammation was unknown. A single careful pathologic study showed that the parasite *Toxoplasma* was encysted within the inflammatory scar in such eyes. This identification of cause has led to appropriate therapy for this disease.

Although Bruch's membrane appears at first glance to be an inert layer separating pigment epithelium from choriocapillaris, recent studies suggest that its failure may play a role in macular degenerative diseases.[88,119] Of particular importance is the study of alterations in Bruch's membrane that result in the formation of holes or cracks and thus permit direct access of the choriocapillaris to the pigment epithelium.

Immunity

In the past several years there has been a greatly increased awareness in clinical ophthalmology of the role of the immune response.[124] As a result, it is now known that in many instances the precise grading and degree of host response can vary, and that it is this variation that controls the clinical expression of the disease.[125] This knowledge, combined with an awareness of the choroid and iris' well-established predilection to inflammation, mandate a substantially enlarged effort in ocular immunology.

Priorities and Recommendations

- Compare the anatomy of the central and peripheral choroid
- Investigate the effect of aging on the choroid and Bruch's membrane
- Undertake clinicopathologic correlations in donor eyes
- Study uveal hemodynamics
- Search for an angiogenesis factor in uveal neovascularization
- Culture uveal tissue for biochemical investigations
- Study mechanisms of immunogenic inflammation: antibody-complement mediated reactions and cellular immune reactions

- Conduct further studies of the nature of several systemic immunologic diseases, such as rheumatoid arthritis, associated with uveal tract inflammation to develop more effective therapy of both the ocular and systemic manifestations
- Investigate auto-allergic disease of the uvea, especially with respect to antigens of the lens, retina, and retinal pigment epithelium
- Determine the nature of the host response to infectious agents (virus, bacteria, protozoa)

Resource Requirements

Currently there are no NEI grants for research in the *Uveal Tract*. The Panel recommends that 18 research projects be funded in FY 1978 at an estimated total cost of $1,401,000. Additional manpower will also be required to carry out the above research program. This will involve the specialized training of currently active scientists as well as the recruitment and support of young researchers entering the field. Special needs exist in basic immunology and in the physiology of transport and permeability.

9

Vitreous Humor

THE VITREOUS OCCUPIES approximately 80 percent of the volume of the eye (see Figure 12). It is generally thought to play a relatively passive role in ocular physiology, permitting light waves to travel unimpeded through its transparent body from lens to retina while acting as an internal support.

Recently, it has been learned that the surgical removal of the vitreous humor, if properly performed, carries with it few deleterious consequences.[126] This finding is of great clinical importance, for although the vitreous receives minor attention in health, it assumes considerable significance in disease. Any of a number of disorders—for instance, diabetes mellitus, intraocular infection, and uveitis—achieve their full potential for harm as a result of changes wrought in the vitreous.

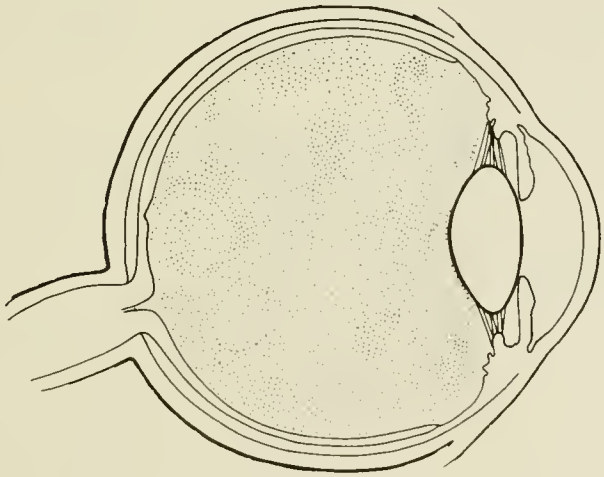

Figure 12. The vitreous humor (shaded area) fills 80 percent of the eye's volume.

Diabetes mellitus serves as an important example. A key and tragic occurrence in the progress of diabetic retinopathy is the breakdown of small retinal blood vessels. When this happens, blood flows into the vitreous humor and vision is immediately impaired; light cannot get through the vitreous to the retina. Moreover, blood in the vitreous acts as an irritant, causing a vitreous scar to form that by itself can permanently hamper clear vision. Worse still, by contracting,

such scars pull the retina away from its normal position—that is, they detach the retina.

A similar train of events can follow vitreous hemorrhage from trauma, from sickle cell retinopathy in young adults, or from the vascular complications of retrolental fibroplasia of infants.

Most investigators believe that the vitreous plays a major role in the common types of retinal detachment, either through inertial traction leading to a break in diseased retinas or pure traction following shrinkage or collapse of the vitreous[126] (see Figures 7, 8, 9). Even healthy retinas may develop tears or holes following trauma if the vitreous is bluntly displaced. Vitreous reaction to surgical repair of retinal detachment procedures may, in some cases, lead to what is called massive vitreous retraction, an irreversible process that makes further repair difficult, if not impossible.[127,128]

Intraocular foreign bodies and inflammations, including infections, also produce significant visual morbidity. Here again, the vitreous reacts to such insults by fibrous proliferation and by retraction, leading to retinal breaks and retinal detachment.[129]

Developmental errors affect a smaller number of patients, but are nevertheless tragic because they occur in children. The most important conditions of this type include persistent hyperplastic primary vitreous and inherited degenerative disorders. It is also probable that vitreous malformation plays a role in retinal dysplasia.

The public health importance of vitreous disease can be estimated from national statistics on their frequency. Approximately 25,000 persons suffer retinal detachment each year; it is estimated that approximately half of these cases result primarily from vitreous disease. It should be recognized that vitreous disease may be secondary to another defect such as diabetic retinopathy. At present, the sight of over 300,000 Americans is threatened by diabetic retinopathy alone (see Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*).

The prevalence of retrolental fibroplasia in 1972 was 19,000 cases, all of which were considered to cause severe visual impairment; more than one-half of these cases caused legal blindness. Sickle cell retinopathy accounts for a tragic number of new blindness cases each year.

By themselves these numbers do not express the heavy socioeconomic burden on society or the extreme financial and personal stress that individuals who are blind or who have impaired vision must bear.

Accomplishments

A good start has been made in advancing knowledge of the structure, composition, and function of the vitreous body. Most of these advances have been made with the support of the National Eye Institute.

It is now well-established that the vitreous is a collagen gel formed of fibrils of protocollagen, reinforced by giant molecules of hyaluronic acid. The vitreous cortex is sparsely populated with vitreous cells whose function is not entirely understood. The physiological role of the vitreous, aside from keeping the center of the eye transparent, is only partially understood. It functions as a barrier to invading cells or large molecules and acts as a shock absorber to protect the delicate retina.

Vitreous research has also made substantial progress from a clinical standpoint. Clinical examination of the vitreous has improved with the development of better slit lamps, improved diagnostic contact lenses, and a careful choice of the appropriate wavelength of light for illumination of the

vitreous structures. Findings made by slit lamp microscopy can often be confirmed by refined techniques such as ultrasound examination.

Currently, there is a strong emphasis on disease-oriented vitreous research, brought to the fore largely by the development of instruments that permit mechanical extraction of the vitreous (vitrectomy). This technique has been developed considerably in the past 15 years. Instruments have been developed to cut vitreous membranes, extract vitreous foreign bodies, close abnormal blood vessels, and most importantly, to remove diseased vitreous. One such study is the new national collaborative Diabetic Retinopathy Vitrectomy Study. In it, the effect of vitrectomy performed soon after severe vitreous hemorrhage from proliferative diabetic retinopathy is compared with vitrectomy performed up to one year later. By randomly assigning eligible eyes either for early or late vitrectomy and carefully measuring the visual results and the incidence of complications, this clinical trial, supported by the National Eye Institute, is attempting to find out which is the more effective, early or late. In addition, indications for and complications of vitrectomy in a wide variety of disorders are under intensive study.[130-132]

Current research also includes histological studies of the vitreoretinal junction,[133] the origin of the cellular components of vitreous membranes,[134-136] and the nature of vitreous reactions to trauma. These studies will define the extent and origin of tissue reactions in the vitreous, thus allowing more rational design of treatment.

Interest also continues strong in the search for vitreous substitutes in the form of viscous liquids, gels, and gases for the treatment of retinal detachment[137,138] (see Chapter 6, *Retinal Detachment*).

Research Objectives

- Enhance basic understanding of the vitreous
- Improve present techniques for diagnosing and treating vitreous disease
- Seek new ways to manage vitreous disease

Research Needs and Approaches

The research needs in this subprogram may be subdivided into two broad categories: research aimed at increasing understanding of the nature and functions of the vitreous, and research aimed at improving the ability to cope with vitreous disturbances.

Nature and Functions of the Vitreous

There are five important areas in this type of research that offer unusual opportunities at this time.

Importance of the Physical State of the Vitreous

Vitreous humor can be either a gel or liquid. The best example of a healthy liquid vitreous is that found in the owl monkey. There is a striking difference

between the reaction to chemical or traumatic insult by a liquid and a gel vitreous. Damage to the structure of the vitreous gel causes serious pathological changes. The reasons for this should be fully elucidated. The role of hyaluronic acid in vitreous liquefaction during disease must be clarified. Particular attention should be paid to the relation between the macromolecular composition of the vitreous gel and its physiological and pathological reactions.

Role of Cells in the Vitreous

In tissue culture, vitreous cells synthesize glycoproteins, glycosaminoglycans, and to a small extent, hyaluronic acid. The origin, function, and metabolic changes that occur with aging of these cells are largely unknown. They are obviously the metabolic centers of an otherwise nearly acellular tissue. They may be responsible for aging changes, and they may participate in massive preretinal retraction. Vitreous cells should be further studied in tissue culture and in vivo.

Immunological Role of the Vitreous

Very little is known about the immunogenicity of the vitreous in different species. Delayed release of intravitreously-injected antigens leads to recurrent uveitis. The vitreous cells, including macrophages, could play a major role in the immunological response of the vitreous and contribute to the persistence of uveitis. Therefore, vitreous macromolecules (e.g. proteins and glycoproteins) and vitreous cells in uveitis should be studied immunologically and biochemically.

An experimental animal model was recently discovered for peripheral uveitis.[139] It is important to determine the role played by the vitreous gel and by the ciliary processes in the development of this disease. One should remember that in humans this disease mainly affects young people, that its cause is unknown, and that no effective therapy is presently available.

Permeability and Metabolic Studies

The precise way in which cells and molecules from the blood gain entrance to the vitreous gel is practically unknown. This is certainly an important factor in the metabolism, regeneration, and immunological complications of the vitreous gel. Disturbances in the blood-ciliary body-vitreous barrier can lead to vitreous pathology and in turn to disorders in the adjacent tissues (e.g. cataract formation and uveitis). Therefore, permeability and metabolic interaction of the vitreous humor with adjacent tissues, particularly the ciliary body and lens, should be studied. Similar relationships between the retina and the vitreous humor have not been studied in sufficient detail in spite of their obvious possible relevance to the development of proliferative diabetic retinopathy and related diseases. (See Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities.*)

Regeneration Processes

In the owl monkey, which has a liquid vitreous humor, full regeneration of hyaluronic acid has been demonstrated. Nothing is known about the process or

extent to which gel vitreous regenerates. Disorders in this regenerative process and its regulation may well be the cause of some types of severe pathology. These problems should be studied using gel and liquid vitreous models in vivo, and tissue culture techniques in vitro for vitreous cells.

Research in the Management of Vitreous Diseases

Permanent Implants

The effect of injecting viscous liquids into the vitreal cavity (including hyaluronic solutions) has been studied. However, such effects are poorly understood. The advantages that vitreal implants would offer in the treatment of severe cases of retinal detachment are well recognized. The effects of implants on residual vitreous gel, vitreous cells, and adjacent tissues need to be studied.

Pathological Studies

Much retinal pathology derives from the formation of membranes and blood vessels within the vitreous humor. The source and nature of preretinal and vitreous membranes need to be investigated. Equally important, the part played by the vitreous humor in pathological new blood vessel formation in the retina must be studied. The role of hemorrhage in producing vitreous scarring must be anatomically and biochemically defined, as should the nature of the subsequent reactions that lead to scar contraction.

Also important to progress in the management of vitreal disease is documentation of the long-term effects of its mechanical removal. Useful clinical observations will no doubt be accumulated from the collaborative Diabetic Retinopathy Vitrectomy Study, but it will also be important to document basic cellular and molecular reactions. Obviously, such documentation must be based upon prior metabolic studies of normal vitreous such as those emphasized above.

Surgical Treatment

As the vitreous humor has increasingly become more accessible to the surgeon, new and important needs have arisen. Further data and experience are required in the treatment of the vitreous humor after severe ocular trauma and penetrating injuries. There is also substantial need for the development of new and better surgical instruments to make surgery in this region less hazardous and more efficient. Improved microinstrumentation for vitreous removal is especially needed as are a wider variety of intraocular probes for foreign body removal and coagulation of bleeding vessels. There is substantial opportunity here for the application of modern physical technology. When it is not possible to look through a clouded vitreous to see the retina behind it, it becomes imperative to find alternative means of visualizing the retina. One step in this direction is dynamic ultrasonography during operative procedures where sound waves bouncing off the retina and its contents are translated into a visual image, allowing the surgeon to operate more safely when direct visualization is not possible. It should be noted that ultrasound already has been applied preoperatively to great advantage. With further refinement, it could become a practical aid during surgery.

Treatment of Infection

Infection of the vitreous humor presents a special hazard. It has recently been suggested that the most effective mode of therapy is direct injection of antibiotics into the vitreous.[140] However, the efficacy and risks of this procedure are not fully established. This method has not been proven to be the method of choice. Moreover, once injected, antibiotics diffuse directly into the neighboring retina. Since they have profound chemical and metabolic effects, antibiotics can in certain cases poison the retina. Thus, it is very important to test the retinal toxicity of different antibiotics injected into the vitreous of animals.

It is likewise important to test the efficacy of particular antibiotics or combinations thereof in combatting specific types of vitreous infections. In addition, the effect of performing vitrectomy before beginning drug therapy for endophthalmitis should be compared with drug therapy alone.

Priorities and Recommendations

- Continue anatomical and morphological studies of the vitreous
- Further explore the biochemistry and metabolism of the vitreous
- Conduct morphologic and metabolic studies of the vitreous-retina, vitreous-lens, and vitreous-ciliary body interaction
- Study the role of the vitreous in immunologic reactions of the eye
- Study vitreous reaction to trauma (including surgery)
- Study age-related biochemical changes in the vitreous
- Delineate the needs and indications for vitreous substitutes
- Study the effects of available antibiotics on the vitreous and retina
- Improve techniques and instrumentation of surgical treatment of vitreal disease

Resource Requirements

In FY 1977 there will be approximately 13 research grants funded by the NEI in studies of *Vitreous Humor* at a total estimated cost of $841,000. The Panel recommends an additional 18 research grants, one specialized clinical research center, and one research contract to be initiated in FY 1978. Total estimated funding for this subprogram in FY 1978 will be $2,750,000.

10

Visual Cells and Pigment Epithelium

THE MOST SPECIALIZED cells in the visual system are the photoreceptors—the rods and cones (see Figure 13). The outer segments of the rods and cones contain the visual pigment which makes it possible for them to receive a light stimulus. As soon as light hits the outer segment, it is absorbed and converted to an electrical signal that is transmitted to the neural network of the retina. Rods and cones are embedded in the pigment epithelium, a cellular lining which separates the photoreceptors from the blood capillaries of the choroid. Under certain circumstances the photoreceptors may be torn away from the pigment epithelium. When this happens, a retinal detachment has occurred. Loss of vision follows.

The photoreceptors and the pigment epithelium are the basic elements of the visual process, and their death or malfunction is at the root of many blinding diseases. These include developmental and degenerative disorders such as retinitis pigmentosa and macular degeneration, retinal detachment and circulatory disorders, as well as disorders induced by drugs, by blood-borne abnormalities, or by nutritional deficiencies. Thus, research in this subprogram is applicable to many eye diseases. It is directed toward understanding basic properties of the photoreceptors and pigment epithelium in normal states and in animal models of specific retinal diseases.

Accomplishments

During the last three decades, extraordinary advances have been made in understanding the structure, chemistry, electrophysiology, and cellular biology of the photoreceptors as well as of the pigment epithelium. Research success continues apace, providing a base of information from which improvements in clinical eye care are constantly evolving. The following facts seem now to be well-established:

The outer segment, the photoreceptive part of the visual cell, is made up of an orderly stack of discs or folds of bilayered lipid membranes which provide a matrix for protein molecules. These proteins are mainly the light-catching visual pigment molecules: rhodopsin in the rods, cone pigments in the cones.

Retinal, a derivative of vitamin A, is bound to the protein of the visual pigment and gives the molecule its color and its specific ability to catch light. Once light is

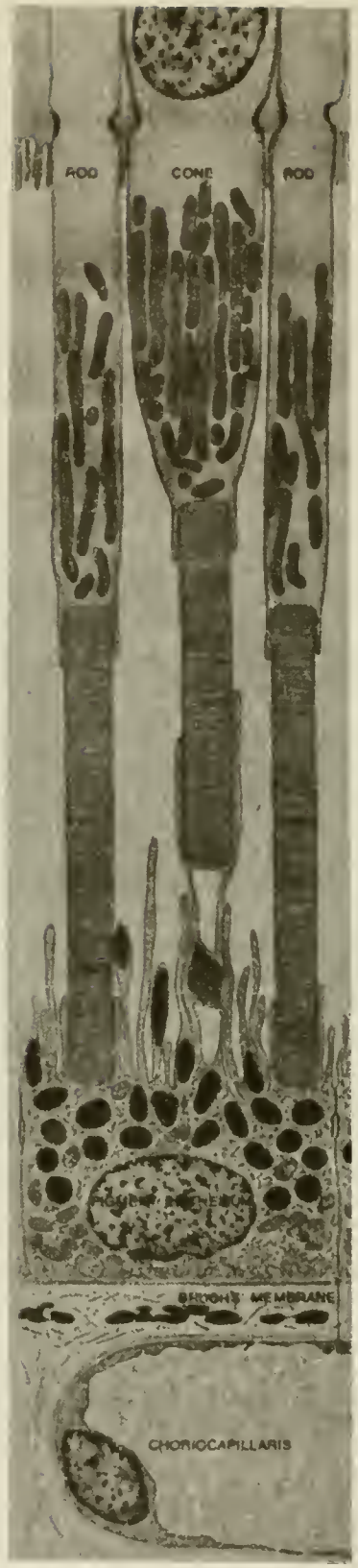

Figure 13. Schematic drawing of the visual cells and pigment epithelium.

caught, the pigment molecule undergoes several color changes. Although the identity and the mechanism of the change which triggers an ionic permeability signal in the outer segment membrane remain to be specified, the result is clear: light is transduced into an electrical charge which initiates the flow of information from the photoreceptors to the brain.[141,142] This process may be rather demanding on the structure of the visual cells, for it is now known that the outer segments are regenerated continually. The new discs form at the base and old ones are shed from the tip.[143] The nearby pigment epithelium "eats" these old discs by phagocytosis and digests them.[144]

The choroidal side of the pigment epithelium is a specialized receptor surface for vitamin A which is carried to it by the blood as a complex with a specific protein.[13] The pigment epithelium is also a storage site for the recycling of vitamin A from light-bleached rhodopsin.[145]

The pigment epithelium controls many nutritive exchanges between the blood and the photoreceptor cells. It is firmly attached by Bruch's membrane to the choroid which is rich in blood capillaries. This is important because blood capillaries are absent in the layers of the retina occupied by the well-ordered photoreceptive cells.

The visual cells and the pigment epithelium may have unique properties because in transducing light of various intensities, colors, and patterns into neural information they serve a unique sensory function. These unique properties include metabolic and synthetic activities, membrane composition and dynamics, as well as specific vulnerabilities to chemical and physical agents.

Specific functions and structures of the visual cells appear to be controlled by specific genes. Single gene mutations in animals and man are responsible for hereditary visual cell dysfunction or markedly reduced visual cell viability. Animals afflicted with hereditary retinal degeneration have recently become the subject of intensive investigation. As a result, an active search is underway to relate the precise mutation responsible for visual cell degeneration in mammals to the primary failure of a specific function of the visual cells or the pigment epithelium cells. It is very probable that all specific disorders of these cells relate to their unique sensory function and properties. New techniques, new models, and new concepts are being applied to advance studies of the normal and abnormal functioning and structure of these cells. Future research should accelerate understanding of these attributes and provide new knowledge to be applied to the prevention and treatment of retinal diseases.

Research Objectives

- Learn more about the normal visual process as it relates to biochemical, physiological, and structural properties or activites of the photoreceptor cells and the pigment epithelium, and of the cooperative interactions of visual cells and pigment epithelium
- Understand prenatal and postnatal retinal development and the mechanisms and influences which maintain the adult, differentiated cells in their normal functional state
- Discover in animals the causes of specific degenerative disorders or dysfunctions of visual cells and pigment epithelium
- Learn of enzymatic reactions or membrane properties on which the functional and structural integrity of visual cells and pigment epithelium critically depend and which thus could be the prime target of destructive or inactivating disease processes

Research Needs and Approaches

It has now been established that rod and cone outer segments are continuously renewed and that shed packages of old discs are digested by the pigment epithelium.[143,144] In the past two years it has become apparent that light may play a pivotal role in controlling the renewal and shedding processes.[146] Further work is required to understand the mechanisms by which light exerts the control of these processes as well as of others on which the continuous maintenance of the normal functional state of the photoreceptors depends.

Phagocytosis is a multistep operation involving recognition, engulfment, and formation of digestive bodies.[147] Phagocytosis by the pigment epithelium of shed outer segment discs is absent and causes accumulation of outer segment debris in the RCS (Royal College of Surgeons) strain of rats with hereditary retinal degeneration.[148] Biochemical, histological, and tissue culture work must be extended in order to determine what controls the specific phagocytic activity of the pigment epithelium and where this can go wrong.

Evidence has accumulated that rod outer segment function may be affected by essential fatty acid deficiency.[149] There appears to be a complex mechanism centered in the inner segment of the photoreceptors that regulates the rate of outer segment renewal. It is conceivable that nutritional factors[150] and illumination[151] may slow or accelerate the rate of photoreceptor degeneration. All factors which may influence synthetic processes of the visual cells or their specific parts, especially their membranes, deserve extensive studies for which much groundwork has been laid in many areas of molecular biology. Work on the isolated retina[152] is also valuable because the surrounding medium is easily modified.

The rod outer segment consists of membrane layers containing the photopigment rhodopsin which transmits the light stimulus. X-ray diffraction studies, electron-spin labelling, fluorescent labelling, freeze-fracture and other refined techniques, including a study of artificial membranes, are presently used to determine the position of rhodopsin within the membrane, the locations of its functional sites, and the dynamics of its interactions with the lipids of the membrane.* Autoradiography is used for measuring the incorporation of protein in the outer segment membrane as well as for the determination of lipid turnover and distribution.

All present and past studies suggest that visual excitation is triggered by a conformational change of the rhodopsin molecule in response to the isomerization of the chromophore (retinal) by light.[141] The transduction mechanism appears to require a transmitter from the discs to the limiting membrane and it has been suggested that this messenger is calcium.[142] Phosphorylation of rhodopsin may play a role in photoreceptor adaptation as may calcium and the cyclic nucleotides. The concentration of guanosine 3′,5′ monophosphate (cyclic GMP) associated with the rod outer segment is reduced by illumination, probably because its breakdown by the enzyme phosphodiesterase is activated. Cyclic nucleotides also may control vital photoreceptor cell functions. For mice which are homozygous for the retinal degeneration gene, an abnormality in retinal GMP precedes the death of the photoreceptors.[153]

*Although of immediate pertinence to this report, the series of investigations referred to in this paragraph are so extensive in number and so diverse in type, that it is not possible to give even a reasonable sampling of references under the present format. Instead the interested reader is referred to H.J.A. Dartnall (ed), *Photochemistry of Vision, Vol VII/1*, "Handbook of Sensory Physiology," Berlin, Spring-Verlag, 1972.

The pigment epithelium is involved in a number of cooperative functions in photoreceptor physiology. As changes in its transepithelial electrical potential indicate, it is probably involved in controlling the ionic milieu of the photoreceptors. At present, its electrogenic properties and permeabilities are analyzed in the isolated epithelium.[154]

The role of the pigment epithelium in the blood-retina transport of vitamin A and in the recycling of retinol is being very actively studied. Specific receptors have been discovered at the choroidal surface of the pigment epithelium for the retinol-binding protein which transports retinol in the blood. At these sites, vitamin A is delivered to the pigment epithelium.[13] Further, it now seems clear that other specialized protein transport systems are present within the pigment epithelium itself and with the photoreceptors, as well as *between* these two groups of cells. Some are specific for particular derivatives of vitamin A.[155] These have yet to be properly localized and characterized.

At one time, it was assumed that the pigment epithelium contained an enzyme that isomerizes vitamin A from the *trans* to the 11-*cis* form. New evidence supports the idea that the isomerase is in the rod outer segment and may be specific for the vitamin A ester which the pigment epithelium provides for photoreceptor use.[145] The cone system is poorly understood and does not seem to be critically dependent on the pigment epithelium.[156] In rod outer segments, the chemical pathways of rhodopsin bleaching and regeneration involve at least five enzymes and their characterization is an important future task.

A recent study on experimental chimeric rats of the RCS and normal strains suggests that the pigment epithelium provides chemical factors which sustain the viability of the photoreceptors.[16] Influences of this kind are known in neuron-to-neuron relationships (trophic factors) and may be of critical importance in retinal degeneration, thus they deserve intensive study.

Cone cell bodies survive the death of the rod cells and the degeneration of the cone outer segments in animal models of retinitis pigmentosa. These cell bodies continue to have synaptic contact with horizontal and bipolar cells. This survival seems responsible for the now well-established fact that animals with advanced retinal degeneration have surprisingly well-maintained vision.[157] In human patients, residual photoreceptive capacities may also exist. Studies of this capacity in the animal models should provide information which may greatly influence the management of patients with advanced retinal disorders.

The study of selective photoreceptor and pigment epithelium degeneration caused by drugs and poisons has been useful for determining specific vulnerabilities of retinal cells and in defining critical areas for future research in the pathology of retinal diseases. Over the past few years, it has been shown that light in amounts exceeding that of an animal's normal habitat destroys its photoreceptors, especially after long periods in a dim environment.[27] This damaging effect of light on the photoreceptor, as studied in rats, may be associated with the degeneration of the pigment epithelium. Light also accelerates the progress of hereditary retinal degeneration in RCS rats. These findings open up a new field for investigation and mandate study of the effects of light on people with macular degeneration and retinitis pigmentosa.

The study of animal models of human retinal diseases is a prerequisite for advances in the management and prevention of these diseases. Inherited diseases of photoreceptors and pigment epithelium are known for rat[16,148] and mouse strains,[153] dog breeds,[158] and for baboons.[94,159] For technical reasons, and for reasons of cost and availability, none of these genetic disorders has been studied thoroughly enough to determine the mechanism of disease. Information derived from such animal models is essential in the search for the cause and treatment of almost all types of retinal and choroidal disease.

Priorities and Recommendations

- Study the retinal photoreceptive capacity in advanced stages of retinal degeneration
- Study in animal models the mechanisms which determine the manifestations of specific retinal diseases
- Study the interactions between photoreceptors and pigment epithelium including the characterization of trophic influences
- Study the controls exerted by light and nutrition on metabolic and synthetic activities of photoreceptors and pigment epithelium
- Investigate the role of calcium, cyclic nucleotides, hormones, and other cell products in controlling the properties and functions of the visual cells and pigment epithelium
- Study all aspects of photoreceptor membrane development and renewal
- Elucidate the physical and chemical, and dynamic and static properties of the membranes of photoreceptors and pigment epithelium

Resource Requirements

An estimated 96 research grants concerned with *Visual Cells and Pigment Epithelium* will be awarded by the NEI in FY 1977 at a cost of approximately $6,213,000. The Panel recommends that an additional 16 research grants be funded in FY 1978 bringing the total estimated funding of this subprogram to $7,458,000. See the tables at the end of this report for details. Also, see the end of the next chapter, *Retinal Organization and Visual Adaptation*, for a discussion of the importance of developing financial and manpower resources in both these vital areas of basic visual science.

11

Retinal Organization and Visual Adaptation

THE PERCEPTION BY the brain of visual information depends on the orderly receipt of a visual image by the rods and cones, the photoreceptor cells of the retina. However, the retina is much more than an array of photoreceptors. Before the visual signal generated by the rods and cones leaves the eye, it must pass though a neural network made up of four different types of nerve cells. These four types of retinal neurons, the precise connections of which are still not completely known, are actually a part of the brain located within the eye. A significant amount of neural processing occurs within the retina. In fact, the basic response of neurons throughout the visual system—impulse discharges at either the onset or cessation of a light stimulus, depending on its nature—is established within the retina.

Thus, an understanding of retinal organization is requisite to any significant understanding of how we see. Since the retina is also part of the brain, any understanding of the retina also provides clues concerning brain mechanisms.

An example of this is the widespread interest in the pharmacology of the retina. It has already been shown that five different neurotransmitters may be at work in a single plexiform layer. These transmitters—acetylcholine, dopamine, gamma-amino-butyric acid, glycine, and serotonin—are also thought to be major neurotransmitters in the vertebrate brain.

It should be added that the retina shares other properties with the brain. For instance, just as the brain blood vessels control access from the bloodstream to brain tissue, preventing the passage of some substances while aiding the passage of others, so too the retinal blood vessels constitute a selective barrier mechanism. And, just as there is a close cooperative relationship between the nerve cells and the glial elements of the brain, so is there a similar relationship in the retina. Little wonder then that more and more brain researchers are turning to the retina because, in reality, it is an accessible piece of brain tissue.

Earlier chapters of this report have addressed the various diseases of the retina and their impact on the individual, his or her family, and society at large. Their costs in medical, social, and economic terms have been presented. Fundamental to the prevention, diagnosis, and treatment of these diseases is a basic understanding of retinal organization and visual adaptation. This chapter discusses the current state of knowledge and future research opportunities in this field.

Accomplishments

Over the past two decades, spectacular progress has been made in unraveling retinal mechanisms. As a result, the retina may be the best understood part of the vertebrate central nervous system. However, much needs to be done before a completely satisfactory understanding of the retina is attained. Also, a good deal of information has been derived from studies on cold-blooded vertebrates, but so far such investigations have not been extended to mammals and humans. This, of course, is essential if realistic answers to clinical problems are to be provided. The potential gains from further research are enormous.

Research Objectives

- Define the principles behind the organization of the neural retina
- Specify the conditions necessary for the maintenance and proper functioning of the retina
- Develop noninvasive (harmless) techniques by which retinal function in humans can be measured

Research Needs and Approaches

Retinal Anatomical Studies

The cellular organization of the retina was first described a century ago and has been elaborated by many researchers in ensuing decades. However, virtually all studies prior to 1950 were limited by the resolution of the light microscope which does not permit visualization of the junctions between cells and thus does not yield a realistic idea of the pathways through the retina. The development of the electron microscope fostered a renaissance in retinal anatomical studies. With today's instruments, resolving power exists far beyond that needed for such studies. Many of the junctions between retinal cells have been identified, more are being recognized each day, and qualitative diagrams (Figure 14) are being deduced.

Retinal Function

The construction of precise, quantitative "wiring" diagrams of vertebrate retinas is virtually within the reach of present technology or slight modifications thereof. For example, silver staining of neurons can be combined with electron microscopy to correlate cellular and synaptic organizations,[160] and computer-assisted analysis of serial sections can reduce to manageable proportions the enormous amount of detail contained within just a small bit of neural tissue such as the retina.[161] In addition, newer techniques such as freeze-cleave may permit the recognition of excitatory or inhibitory synapses in the plexiform layers of retinas,[162] or techniques such as the Falck-Hillarp method which identifies neurons that contain particular neurotransmitters may help elucidate chemical-specific pathways.[163] The importance of these studies cannot be overemphasized. Many detailed aspects of human retinal function, both normal and diseased, can be understood only by careful anatomical examination.

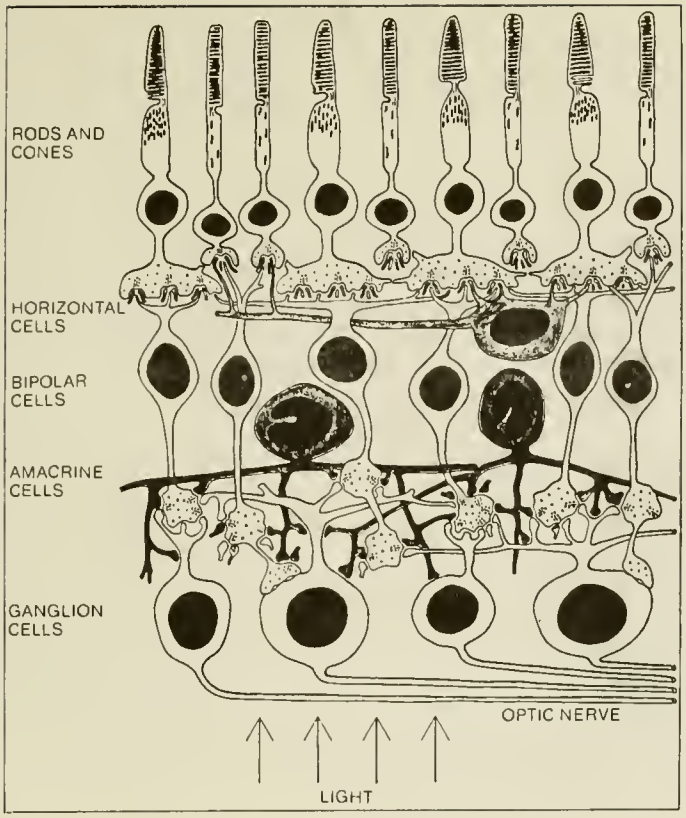

Figure 14. Organization of the primate retina.

Figure 14 shows the neural cells of the primate retina and how they connect with one another. Note that the pathway from the receptors to the ganglion cells is far more complex than a simple through-line. Horizontal and amacrine cells, for example, extend widely across the retina making connections with receptor cells, bipolar cells, ganglion cells, and occasionally with each other. The output of the retina, the optic nerve discharge, thus reflects a composite of activity from all the types of retinal cells.

Electrical Activity and Visual Function

Electrical activity was first recorded from the eye over a century ago. The electroretinogram (ERG) is a gross, complex series of electrical potentials which are now known to arise partly from the receptors, partly from other retinal cells, and partly from the pigment epithelium. The ERG is without doubt the most extensively studied electrical potential related to the visual system, and although it is still imperfectly analyzed, it can provide important information about visual function (see Chapter 1, *Developmental and Hereditary Disorders*, and Chapter 6, *Retinal Detachment*). Since the ERG is a noninvasive probe, its clinical importance undoubtedly has been only partially realized.

The first single unit recordings of electrical impulses from the retina were obtained in the late 1930's from individual nerve fibers that had been dissected from the retina. Shortly thereafter, metal microelectrodes were developed that allowed the recording of impulse activity from single cells. This technique has

since been employed widely in retinal studies, primarily because the retinal ganglion cells positioned on the surface of the retina are exceedingly accessible to such probes. Thus, today there is considerable information on the output characteristic of ganglion cells in a wide variety of vertebrate species, including primates.

Intraretinal Mechanisms

Of all the retinal neurons, only the ganglion cells use impulses exclusively to transmit information.[164] Cells distal to the ganglion cells mainly employ sustained, graded potentials, either partially or wholly, to signal information. Such potentials are not readily recorded with metal microelectrodes. Understanding of intraretinal mechanisms awaited the development of intracellular recording techniques with glass micropipettes. Such techniques have been available only within the past two decades, and this research area is, at the moment, one of the most active and exciting in all of vision research. As yet, virtually all projects have been done in cold-blooded vertebrate species, such as mudpuppies, turtles, and goldfish, where such studies can be more readily accomplished. Similar studies in mammals are just beginning. However, it is already clear that the electrical activity of identified, single retinal neurons can be recorded. The information so obtained is the key to understanding how the retina processes visual information, opening the door as it does to a host of studies on synaptic, cellular, and pharmacological interactions.

Biochemistry of the Retina

Using electrical measurements to monitor information transfer through the retina presents a view of retinal function in terms of changing currents, potentials, and resistances. But concepts of retinal function should not be fettered to what instruments can measure now. A more encompassing view would interpret the information transfer in terms of the complex trains of causally related chemical events that spread through the retina in response to a change in illumination. Only some of these give an electrical sign, i.e. changes in membrane constituents that affect the active or passive movements of ions, but many of them do not, e.g. most of the steps involved in synaptic transmission. In order to understand the mechanism of normal function and the pathogenesis of disease, investigations of these excitable chemical processes must continue. Studies of the "back-up" metabolism that maintains the conditions necessary for their operation, e.g. generation of ATP and synthesis of macromolecules, must also continue.

Four areas of retinal biochemistry seem particularly promising for further investigation at this time because they are intimately related to function (and therefore to malfunction) and are experimentally approachable:

1. *Neurotransmitter chemistry* including identifying the rate-limiting steps in synthesis and the control thereof and characterizing the processes involved in packaging, releasing, receiving, and removing the neurotransmitter.

2. *Energy metabolism* which is peculiar in retina because there are separate oxidative and glycolytic processes and because there is an unusually large store of substrate (as glycogen) in Müeller cells with provision for its release (glucose-6-phosphatase). Dysfunction of energy metabolism underlies a number of important retinal diseases.

3. *Chemistry of ion "carriers" in membranes* including the control of active transport and the regulation of passive flux by calcium ions and by neurotransmitters.

4. *Protein chemistry* including the factors that control synthesis, post-translational modification, and breakdown and thereby determine the role of proteins in the maintenance of homeostasis and in adapting the retina to an altered state.

Experiments on the chemistry responsible for function require a precise control of the chemical environment that can usually only be achieved in vitro. Since the retina is, in the words of C. N. Graymore, a "ready-made tissue slice," it may be a principal vehicle for major new advances in the molecular biology of excitable tissue.

Pharmacology of the Retina

The pharmacology of the retina is a related research area of intense interest at present. However, hard facts on the neurotransmitters just mentioned in the section on biochemistry are scarce. For instance, there is compelling evidence for the location of dopamine within a population of amacrine cells.[165] Evidence for a role of acetylcholine in the inner plexiform layer is likewise strong, but here location is unclear.[166] The cells which release acetylcholine are as yet unknown. The assignment of other transmitter agents to specific retinal cell types is equivocal at best although there is increasing evidence that other neurotransmitters are at work.

Visual Adaptation

A facet of the visual system that has long been of interest is its ability to adapt —that is, its ability to adjust its sensitivity to the prevailing light intensity. Virtually all visual adaptation occurs within the retina, and although early work suggested that visual sensitivity is closely related to the level of visual pigment in the eye, recent work indicates that there are both receptoral and retinal mechanisms involved.[167] Elucidation of the mechanisms underlying visual adaptation is providing clues to the loci of the defects underlying certain night blindness conditions, and current research in this area is beginning to yield results of clinical interest.

Invertebrate Research

A number of important areas of retinal research do not fit into the above discussion, including work on invertebrate eyes. Because of large cell size, accessibility, and sometimes simplicity of organization, certain experiments can be performed with the invertebrate that are still impossible with the vertebrate retina. An outstanding example is the analysis of lateral inhibition in the horseshoe crab eye, which was deemed so significant that a Nobel Prize in Physiology or Medicine was awarded for this research in 1967.[168] Similar research on invertebrates continues to be pursued the world over and is contributing substantially to understanding visual mechanisms.

Priorities and Recommendations

Basic retinal research has been extraordinarily productive over the past two decades, and there is no reason to suspect that its productivity will decline in the near future. The great interest in intracellular recordings from retinal neurons will undoubtedly be maintained, and excellent proposals for future research in this area will continue. However, special encouragement should be given to the following:

- Study intracellular recordings from mammalian retinas. As noted above, virtually all information on intracellular electrical activity of photoreceptors and other retinal neurons has been derived from nonmammalian sources. It remains to be shown whether mammalian retinal neurons function in an identical fashion.
- Study intracellular recordings and pharmacology in combination. Such studies are likely to be particularly profitable in all species and should provide hard evidence on pharmacological mechanisms that is now lacking.
- Exploit modern research methods fully. For example, new studies of the primate retina, especially its central (foveal) region, should be encouraged. Such work should be very profitable and, of course, have particular relevance to clinical problems such as macular degeneration.
- Conduct studies to maintain retinal tissue in artificial and altered environments. This area appears particularly promising, both for elucidating basic retinal mechanisms and for sensible clinical application.[109] The potential for productive research in this area is substantial: it runs the gamut from perfusing whole eyes with artificial solutions while recording from the retinal cells, to growing retinal neurons in tissue culture and observing the formation of synaptic connections between the cells. Only with such perfusion and tissue culture techniques is it probable that necessary physiological and biochemical measurements can be made on human retinal cells. If such techniques can be perfected, it may also be possible to maintain the retina of a patient suffering a period of circulatory occlusion. So far there has been limited but encouraging success in maintaining eyes and retinal tissue in artificial environments; additional work in this area is clearly warranted and should be accorded high priority.
- Study invertebrate visual systems with the same priority as studies on the vertebrate retina. Although such research may appear to be remote from clinical problems, the opportunity for solving certain problems with invertebrates far exceeds what is presently possible with the vertebrate.

Resource Requirements

Research on pigment epithelium, photoreceptors, and neural retina (as discussed in Chapter 10, *Visual Cells and Pigment Epithelium*, and Chapter 11, *Retinal*

Organization and Visual Adaptation) lies at the heart of the entire retinochoroidal research effort. This is evident from the substantial number of funded grants already awarded in these areas. The Panel, after careful study, believes this funding pattern to be entirely appropriate. The present effort is producing results and promises to continue to produce information on the basic functioning of the eye that is prerequisite to the understanding of retinal disease.

Because of the importance of these basic science areas and of the sizeable commitments already undertaken, the Panel has reviewed in detail the current grants in this subprogram. On the basis of this review, there is little question that these grants are of high standard, substantial relevance, and broad scope. As a rule there is relatively little overlap among them, save in one or two special areas. Since the NIH review bodies considering grants are well-informed concerning the total vision research effort, what overlap does exist is in good part necessary and fitting. The Panel believes that a modest degree of overlap with several laboratories working on the same problem is often a spur to action, serving to increase productivity and to move the field very rapidly ahead. It should be added that the Panel was struck by the fact that projects which at first glance look to be similar often on closer inspection diverge in scope and focus.

In reviewing the current grants in basic science of retina and pigment epithelium, the Panel came to the following general conclusions:

Eye research is unusually fortunate in having a large number of able, basic research scientists. For a variety of reasons, many of the best minds in science have been attracted to eye research. The Panel could discern a clear tendency to remodeling; that is, when a longer perspective is taken, it is obvious that the manner of approach to the problems and actual research topics change as new facets of basic science are uncovered. The Panel believes that this is an appropriate response and that this tendency to internal remodeling can be greatly extended. We also think it is imperative to attract the attention of the best research minds already in eye research to neglected areas of opportunity, to many of the urgent needs described in this report. One way to foster this tendency to assume a new focus is through workshops and other types of special meetings. By such means able minds with high scientific faculty can be brought to bear on clinical problems. In short, an overt attempt should be made to attract a proportion of able scientists from areas of greatest scientific strength to areas of current weakness.

The Panel recommends that the same and other mechanisms be used to recruit superior talent from outside the eye research community for the same purpose. The need is greatest for scientists trained in biochemical genetics, biochemistry, and immunology in the search for answers to difficult, outstanding problems in visual pathophysiology.

In keeping with the above, the Panel wishes to emphasize that substantial and, at times, dramatic opportunities for productive research presently exist both in basic and in clinical science. Clearly, recent advances in scientific technique have laid the groundwork for research projects of a scope and an importance heretofore unimaginable. The special qualities of the eye make the retina a practical workshop for projects that have equal relevance to mental health and to neurology. Specifically, the inner retina is a prototype of nervous tissue, a prototype that shares with the brain to a remarkable degree certain metabolic sequences but which is also much more accessible. When the current level of funding of retinal research is viewed in terms of opportunity, areas of weakness, and areas of need, it is clear that an increased level of support is not only fully justified but that it represents an intelligent investment by the public, one that promises to return substantial dividends in improved visual health over the next decade.

The tables at the end of this report provide specific resource requirements for basic science research in *Retinal Organization and Visual Adaptation*. In order to make proper attribution, that is, to indicate the immediate and substantial relevance of basic science to clinical problems in ophthalmology, a proportion of the cost of projects listed under the basic science headings in these tables is attributed to the applicable clinical areas.

In FY 1977 the NEI will fund approximately 63 research grants in *Retinal Organization and Visual Adaptation* costing an estimated $4,079,000. The Panel recommends an additional 14 research grants at an estimated cost of $1,090,000 for FY 1978, bringing the total for this subprogram to $5,169,000 in that year.

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Special Areas of Future Interest

IN THE PRECEDING chapters the Panel has outlined its recommended research approaches and priorities for the 11 clinical and basic subprograms in *Retinal and Choroidal Diseases* which are currently supported by the National Eye Institute. Beyond these opportunities lie areas of future interest which have yet to receive the special recognition they deserve. Nevertheless, they are important. These special areas are:

- Toxic and Environmental Disorders
- Low Vision
- Retinal Regeneration and Transplantation
- Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models

The Panel calls attention to these four areas because there is evidence that they have relevance to large segments of the population and because they are expected to become increasingly important over the next decade.

The Panel believes that the National Eye Institute should initiate and encourage discussions within the Institute and across the community of vision scientists in an effort to delineate clearly the importance of the problems, establish feasible research objectives, identify research needs and approaches, and define the resources required to carry out programs in these areas. Presented below are our preliminary considerations about each area.

Toxic and Environmental Disorders

Importance

Toxic and environmental disorders differ from most of the other clinical conditions considered in this report because their incidence or prevalence cannot be accurately estimated. Yet, from clinical experience and from pertinent research it is known that many drugs, chemicals, environmental factors, and pollutants can damage the eye.

For the retina, the problem of toxicity is two-fold. First, in its susceptibility to toxic agents the retina differs from all other tissues of the body: it has special nutritional requirements, it has an intricate and delicately balanced physiology,

and it functions in a rigorously controlled environment, one with a surprisingly narrow tolerance for change. Although many other tissues have comparable individual limitations, no other tissue has precisely the same vulnerability. Thus, toxic or environmental agents, acting separately or at times together, can exert severely damaging effects on the retina although they are apparently harmless elsewhere. For instance, there is already abundant evidence that drugs that do little or no harm elsewhere in the body can produce a retinal degeneration.[170] There is also evidence that a flash of light, that would have little effect on any other organ, can under certain conditions cause a focal retinal burn.[171] Consequentially, the only tissue that can serve to predict the effect of a given drug or environmental hazard on the retina is the retina itself.

Second, current studies on toxic and environmental disorders of the retina and choroid are inadequate in scope and quality. As a general rule, they are performed outside the eye research community, often by personnel without any special knowledge of the eye. For the most part, these studies are neither supported by nor responsible to the National Eye Institute.

At the root of the problem is the way in which drugs are developed. In the United States, the largest proportion of drug testing is done by individual pharmaceutical companies or by specialized commercial testing laboratories. It is true that in this work, the eye receives substantially more attention today than it did ten years ago. Yet, it is also fair to say that the present level of attention is inadequate. The pharmaceutical companies and testing laboratories usually lack necessary in-house expertise in ocular physiology and pathology. Sometimes they do not even specifically seek out the ocular effects of drugs.

Furthermore, when drugs reach the market, toxic effects on the eye can be subtle or slow to develop. They may not be recognized for what they are—even by an eye specialist unless he or she has some special reason for suspicion. Tests such as dark adaptation, electroretinography, or electro-oculography which might indicate early toxic effects are not routinely done.

A few government-sponsored research activities on toxic and environmental effects are addressed specifically to the eye. The National Eye Institute sponsors a few grants concerned with environmental and toxic effects on the eye. The Food and Drug Administration undertakes specific ocular studies on a limited basis and the Environmental Protection Agency sometimes supports research on the ocular effects of radiation, such as from the laser. The development of new, energy-radiating instruments is largely the province of industrial companies, some universities, and the Department of Defense. However, in sum, the scattered activities that currently exist are inadequate in view of the breadth and complexity of the problem.

Suggested Research Approaches

The Panel urges that steps be taken to ensure:

- *Adequate testing* of all new drugs for retinal toxicity prior to their general release. Long-term studies should be conducted and second-generation effects of drugs should be investigated in animals prior to release for human use.
- *Stringent follow-up* of individual case reports of retinal toxicity resulting either from drugs or from substances added to food.

Newer and higher standards need to be set for the prerelease testing of drugs. For example: for drugs, hormones, preservatives, vitamins, and anesthetics pre-

release toxicity testing should use modern laboratory techniques; have as a defined goal the expert examination of the eye, especially of the lens and the retina; include tissue localization and distribution studies; and specifically, study the effects of each agent on the developing eye. At a minimum, this recommendation demands the establishment of good experimental design with appropriate research protocols and the use of modern testing methods. In effect, it asks for a common sense level of surveillance.

To follow up individual case reports of drug toxicity and environmental hazard to the eye, the Panel suggests that the National Eye Institute establish formal channels of communication with the National Registry of Adverse Drug Reactions[172] recently established at the University of Arkansas for the collection and evaluation of such information. This registry could perform an early warning function by alerting ophthalmologists and the public to toxic agents in general use and to environmental hazards.

There is still too little knowledge of certain aspects of toxic and environmental disorders. Needs in these areas include:

- *Determining tolerable levels of exposure to ambient light.* An increasing body of scientific knowledge on the effects of light on the retina clearly indicates that what has been thought of as safe levels of ambient light may not be safe at all, at least not for certain individuals. The need for better information is especially pressing for individuals with deficient pigment development such as is found in albinism, in those afflicted with hereditary retinal degenerations, in certain types of macular degeneration, and after cataract extraction. Furthermore, in some instances ingestion of certain chemicals may abnormally sensitize the retina to light.

- *Setting acceptable standards for exposure to different types of radiation.* This is a natural follow-up to the above.

- *Tests in animals for toxic and environmental factors.* Animals may or may not show the same susceptibility to drugs as man. A systematic correlation should be made between known ocular toxicities in man and their experimental production in various species of animals. An explanation of any differences should be sought, especially by study of the comparative metabolism of each drug. The use of clinical techniques such as electroretinography and laboratory methods such as tissue culture may help make such testing more productive.

- *Assessing effects of drugs in the developing retina.* Currently, pregnant women, especially those with medical conditions, are given a wide variety of drugs. Yet, in most instances, we do not know the tolerance level of the developing retina to these drugs. Developing tissues can have special and unusual susceptibilities, and toxic effects can occur in minutes. An informed research effort could well herald and thereby avert what would otherwise become unspeakable tragedy.

- *Evaluating the best methods to determine the clinical significance of drug-related changes in retinal function.* Many tests have been used to detect and evaluate toxic damage to the eye. These include electroretinography, electro-oculography, visual fields, dark adaptometry with or without retinal profile testing, macular dazzle, Amsler grid, and color vision testing. In studies of chronic chloroquine administration it has been shown that one of the difficulties in using retinal function screening tests is that the drug can depress the response without causing permanent retinal damage.[173] Ways must be found to predict which few of many patients who have an abnormal response to tests will develop a permanent retinal toxic effect.

- *Determining how drugs damage the eye.* This is a very important area; it promises to provide information that can be used in preventing and treating particular toxic effects. Usually when the toxicity of a given drug to the retina is discovered, a number of investigations are performed simultaneously, depending on the interest generated. However, as interest lessens with time, research often wanes before a complete picture is put together. It would be desirable for some mechanism to be in place to encourage research activity when such lapses occur or when clear conclusions have not been reached.

In sum, principles and practices need to be developed to assure that the greatest benefit and least hazard result from the rapid-fire introduction into our lives of chemical and physical agents, many of which alter the circumstances under which the retina must live.

Other Recommendations

In addition to the broad needs just outlined, other specific, practical needs are to:

- Develop a practical noninvasive oximetry system to monitor the oxygen saturation in the blood of newborns as a means of lessening the incidence of retrolental fibroplasia
- Search out harmless chelating agents to treat retained intraocular metallic foreign bodies
- Study the effect of intravitreal injection of antibiotics on retinal function

Policy and Administrative Issues

The nature of toxic and environmental disorders calls for a series of programs unlike anything the National Eye Institute and the eye research community have been involved with before. Certain policy and administrative considerations need to be resolved in order to develop and support such programs. Some of these are:

- *The role of the National Eye Institute:* Should the NEI participate in an evaluation of the ocular risk of chemical and physical agents? If so, how should the NEI participate? Should the NEI have direct responsibility for evaluating these hazards, or should this function be delegated to outside laboratories or registries supported by the NEI? How can the NEI relate to other agencies such as the Food and Drug Administration and the Department of Defense in evaluating retinal hazards?
- *The capabilities of the NEI:* What additional staff would be required to handle such a program? What additional financial resources would be required? Would an advisory board or committee empowered to define specific research and development projects be appropriate? Would an in-house executive with specific competence in this area be necessary?
- *Mechanisms of support:* Is a special mechanism needed to encourage research on toxic and environmental disorders? Is a special mechanism needed to begin immediate evaluations of potentially toxic agents? How might the NEI coordinate a series of interrelated but separate efforts spanning basic and clinical science?
- *Level of support:* What level of support would be appropriate? Since toxic and environmental disorders extend beyond the retina and in fact encompass all aspects of ophthalmology, how would resources be allocated?

In the face of these considerations, the Panel believes that before detailed recommendations can be made, consideration must first be given to defining the program. However, some projects are imperative and should be funded as soon as possible; the Panel has therefore listed five areas of particular importance each calling for two research grants, for a total of ten, in the tables at the end of this report.

Low Vision

Many persons have sight which has been permanently and irreversibly impaired. Although not totally blind, many have loss of sight sufficient to interfere with gainful employment, limit independent activity, hamper communication, and in general restrict the range of activities that comprise daily living.

The 50-year old accountant with early macular degeneration who can no longer read regular print, the 30-year old housewife with diabetic macular edema who cannot see well enough to manage a household, and the 70-year old widow with glaucoma and cataracts who cannot shop alone differ in type and degree but all are representative of some 1,500,000 individuals with severe visual impairment in the United States.

Although many public and private agencies and individuals are concerned about the welfare of the visually handicapped, research in this area has, unfortunately, been spotty. No single center and no single training program exist which are devoted to the orderly development of ways to improve the visual performance of the partially sighted.

The very few research programs which have been conducted in the past clearly illustrate the potential productivity and merit of such investigations. For example, Dr. Louise Sloan of the Wilmer Ophthalmological Institute at Johns Hopkins Hospital demonstrated in her pioneering low vision clinic that visual performance in certain types of macular degeneration could be improved simply by increasing the contrast on the printed page. In addition, it is now known that laser-generated patterns can penetrate some ocular opacities that otherwise hinder the passage of ordinary light.[174]

To enhance use of the impaired retina and to improve image generation through the clouded cornea or lens, attention should be directed to:

- *Help from bright illumination.* From past work it is known that increased brightness can markedly improve visual acuity in certain stages and types of macular degeneration.[175] Further work must be performed to determine what balance of contrast, color, and border contours give the best possible visual acuity in these conditions.

- *Improved use of the peripheral retina.* Fine visual tasks such as reading are performed by the central retina, usually called the macula, which comprises only 5 percent of the total retina. When the macula is destroyed, as it is in macular degeneration, 95 percent of the retinal area is still intact. The possibility of enhancing the peripheral retina's performance needs to be intensively studied.

- *Magnification.* The use of a hand-held magnifying glass is a traditional and widely-used method of enhancing reading vision for the partially sighted. There are hundreds of types of magnification devices now being prescribed for the partially sighted by optometrists and ophthalmologists, largely on a haphazard basis. Careful studies are required to determine what type of magnification is most appropriate for each sort of visual impairment. The usefulness of magnification devices in combination with modified lighting

and contrast is also important to study. For example, the availability of reasonably priced electronic transfer devices such as units which incorporate closed-circuit television cameras equipped with zoom lenses makes it possible for someone with poor vision to alter at will image size, brightness, and contrast.

- *Laser-generated images.* The full potential and limits of this technique must be determined: What types of patterns and images can penetrate different types of opacities in the eye such as corneal scars, cataracts, and vitreous hemorrhage?[174]

Resource Requirements

The Panel recommends that the National Eye Institute expand its support of research on low vision and on low vision aids. This will require either additional manpower or the shifting of already existing manpower to the task. Perhaps the best setting for such efforts would be one or two specialized centers. This, however, would be very expensive. We estimate, therefore, that four grants in this field with a total cost of $276,000 per annum are justified. There could be a great advantage in cost and efficiency if such grants were awarded to institutions that already have adequate electronic and mechanical shop facilities.

Retinal Regeneration and Transplantation

Almost all of the research needs and opportunities outlined in previous chapters of this report are projects that can be begun immediately or are extensions of work already underway. Almost all are aimed at limiting or preventing damage to the visual system, either by eliminating noxious influences or by employing various types of treatment.

Unfortunately, no matter how successful these efforts are, blindness will always be with us. In fact, if current trends are any indication, there may even be more blindness in the future: to the young from trauma, as ever-increasing types and numbers of motorized vehicles take their toll, and to the old from the cumulative hazards, vascular and others, of a life span far greater in length than common a century and a half ago. As a result, there is an increasing need for some means of renewing or reorganizing damaged eye tissues.

Setting such a goal is a matter quite different from those we have set previously. Either repairing or replacing any part of the serial nerve linkages in the human visual system is not presently feasible. It is a long-term objective for attainment of which two major possibilities stand out: retinal regeneration and retinal transplantation. The two are interrelated.

Retinal Regeneration

Studies in vertebrates on regeneration of the neural retina have focused on two types of phenomena: total replacement of the neural retina and regeneration of parts of certain retinal cells (e.g., visual cell outer segments and ganglion cell axons).

Total regeneration of the neural retina occurs spontaneously in some non-mammalian species. In the salamander, for instance, when the neural retina is removed, the retinal pigment epithelium is capable of regenerating metaplastically an entire, functional neural retina—even in the adult.[176] The regenerated retina sends ganglion cell axons to the brain, each of which terminates in the

tectum at a location appropriate to the position of its ganglion cell in the retina. Thus, in the salamander, the retinal pigment epithelium not only has the ability to transdifferentiate into neural retina, but it also has the information necessary to reestablish an orderly projection of the retina to the brain.

Regeneration of the neural retina from the retinal pigment epithelium also occurs in the domestic fowl;[177,178] however, regenerative capacity is lost relatively early in embryonic development, and the retina regenerates in patches rather than in its entirety. It also fails to reestablish proper connections to the central nervous system. Such differences among species suggest that the ability to regenerate a functional neural retina has been lost in several steps. Were these steps to be identified, it might then be possible to restore to the mammalian retinal pigment epithelium its lost ability to form a new neural retina.

Somewhat less dramatic, but nevertheless of great importance, is the finding that photoreceptor outer segments in primates have special renewal qualities. As shown experimentally in monkeys,[179] rods and cones have a definite renewal capacity: rod and cone outer segments degenerate when retinal detachment is induced; however, if the retina is surgically reattached, the outer segments renew in the following weeks.[180] Little is known about how or why this occurs.

Capacity for renewal of ganglion cells, just as in the case of the retinal pigment epithelium, also varies among vertebrate species. If the optic nerve of a mammal or other higher vertebrate is cut, the entire nerve and its ganglion cell of origin die. However, if the optic nerve is cut in certain lower vertebrates, amphibians and fishes, the optic nerve does not die; instead it regenerates and vision is restored.[181]

Although something is known about the regeneration process, we cannot presently explain why differences in regenerative ability exist among species. Certainly there should be attempts to learn more about this subject. Comparative studies of the developmental biology and chemical embryology of the retina and optic nerve are fully warranted: they could provide insight into the mammalian optic nerve's failure to regenerate when cut.

Retinal or Ocular Transplants

No successful eye transplant has ever been done in a mammal nor is there any near-term prospect for success. However, the subject is of such overriding clinical importance that it merits research attention, since again, there are clear examples of lower vertebrates in which the eye can be successfully transplanted.[182]

At present any effort to transplant a mammalian eye is doomed to failure by the ganglion cell axon's inability to withstand cutting, by the difficulty of insuring adequate circulation of blood to the transplanted eye during or shortly after operation, and lastly, by immune rejection of foreign tissue.

Yet, present limitations do not preclude future advances. Thus, the Panel believes that despite this formidable catalogue of cautions and hazards, a limited and thoughtful laboratory effort should be undertaken. The Panel recommends that support be provided to five new projects in this area in FY 1978. Specific recommendations are listed in the tables at the end of this report.

Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models

In reading this report one repeatedly comes across statements of an insistent need for donor eyes and for animal models. Although objectives of individual

research programs vary, their basic requirements do not: progress in understanding clinical disease depends on the acquisition and study of appropriate human and animal tissues. Since biopsy material from the retina and choroid is unavailable to the research community, it is essential that human eyes enucleated for malignancy or taken postmortem, and eyes from animals with appropriate pathology (that is, pathology comparable to that occurring in humans) become available for study.

The need can be documented in many ways. For instance, there are strong threads of evidence to indicate that at the root of each type of retinitis pigmentosa and, in fact, of each of the hereditary retinal degenerations, there is a specific biochemical defect. If this is indeed true, then comparative biochemical studies of normal and diseased human donor retinas are crucial. So too are comparative biochemical studies of retinas from animals afflicted with hereditary retinal degeneration. The two needs, that for animal and that for human tissues, are interrelated. Not only could the discovery of a specific biochemical defect in animal eyes pinpoint an area for study in humans, but even in the absence of precise overlap in pathogenesis, the existence of animal models opens the door to practical trials of modes of therapy in afflicted animals that could have important applications to humans. It should be added that the animals themselves would benefit if a specific cause for these blinding diseases could be discovered and effectively treated.

Very much the same arguments apply in the search for the cause and treatment of diabetic retinopathy, uveitis, and retinal detachment, and in fact, in the search for the cause and treatment of nearly all the major types of retinal and choroidal disorders with which eye specialists must deal. In searching for the cause of a disorder, there is no substitute for the tissue affected by the disorder.

Granting the validity of this argument, the first question should then be: If there is such an insistent need, why is it not being met? The answer is straightforward: there simply is no supply. In the case of human tissue, the individual laboratory researcher is usually entirely dependent upon the ophthalmology department at his or her own institution. Even when interest is strong within a given department, donor eyes suitable for a specific research project only become available at infrequent intervals. Local resources are usually insufficient.

There is evidence that with proper advertising and collection procedures, eyes with specific pathology can be obtained. At least this has been true in a uveitis research project conducted under the auspices of the University of California School of Medicine in San Francisco. However, even in this, the most successful instance of an attempt by a single group to gather donor eyes on its own, success has been limited.

It should be added that to be of full value, donor eyes need to have two qualities: the specimen obtained must be properly classified and must be treated in a manner appropriate to a specific research protocol. In practical terms this means that the worth of a donor eye is directly related to knowledge of the clinical history of that eye. The more accurately the pathological process is classified and the more completely the precise clinical course and status is documented, the greater is the research potential of an individual donor eye. Similarly, the manner of preservation is important. Frequently, this requires quick freezing and storage at low temperatures or the use of special fixatives and other means of chemical preservation. For electron microscopic observation, such tissues must be fixed very rapidly. If the eye is not so treated, deterioration occurs, and the practical use of that eye is precluded.

In the case of animal models, the cost and the work involved in the acquisition, care, breeding, and distribution of animals with specific pathological conditions is overwhelming to an individual researcher. Only a specific program designed for

this purpose can succeed. That such a program can be mounted and made practical has already been shown by the singular success of the NEI contract for breeding and for distributing to researchers the RCS rat, an animal with a hereditary retinal degeneration.

Thus, there is a broad and largely unmet need in eye research for human and animal tissues. In fairness, it should be added that much of the need is newly-perceived; this rapidly increasing awareness has arisen from the research progress which has taken place in the last decade. During this time there has been a tremendous surge in knowledge of the basic anatomy, physiology, and biochemistry of the retina and choroid. This recently acquired knowledge has made possible studies that could not have even been imagined a decade ago. Without such scientific progress, there really was no opportunity to make proper use of donor eyes and animal models. However, today it is possible to make proper use of such tissue. At present, lack of appropriate tissue stymies research approaches that have already been formulated for many retinal and choroidal disorders.

Given this situation, the Panel considers it imperative that animal models and donor eye programs be given a new dimension and new emphasis. We recommend that the relatively small pilot efforts of the past be expanded to meet the enlarged opportunity of the present and of the future. To do this will require at least six contracts at a budgeted cost of $100,000 each; but the particular nature of this national effort demands organization and attention as much as dollars.

In fact, the Panel envisages quite reasonable costs if it is well-planned and administered. The program must include the enlistment of volunteers to gather and distribute human donor eyes and the active cooperation of ophthalmology centers across the country. Animal models must be searched out and produced in adequate numbers for specific research purposes.

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Project and Resource Tables

Table 1: Retinal and Choroidal Diseases
Total Resource Requirements by Mechanism FY 1978

(Dollars in thousands)

	Research Grants		Specialized Clinical Research Centers		Contracts		Core Centers		Research Career Awards		Research Training		Total
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	Amt.
Estimated Support FY 1977	264	$17,054	2	$ 235	53	$3,403	3	$ 311	19	$489	71	$1,633	$23,125
Additional Requirements FY 1978	236	17,363	15	4,624	20	3,432	5	983	7	185	42	630	27,217
Estimated Total Support FY 1978	500	$34,417	17	$4,859	73	$6,835	8	$1,294	26	$674	113	$2,263	$50,342

Table 2: Summary of Recommendations by Subprogram

	Estimated Support FY 1977				Additional Requirements FY 1978				Estimated Total Support FY 1978			
	Number of Projects				Number of Projects				Number of Projects			
Subprogram	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)
1. Developmental and Hereditary Disorders	16	1	0	$ 1,159	18	2	0	$ 2,051	34	3	0	$ 3,210
2. Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities	40	0	53	5,972	33	3	3	4,092	73	3	56	10,064
3. Myopia	0	0	0	0	15	0	3	1,710	15	0	3	1,710
4. Tumors	11	0	0	712	12	2	0	1,458	23	2	0	2,170
5. Macular Diseases	7	1	0	513	35	2	4	1,583	42	3	4	2,096
6. Retinal Detachment	2	0	0	130	20	3	2	4,086	22	3	2	4,216
7. Inflammatory Disorders	14	0	0	943	18	2	1	2,230	32	2	1	3,173
8. Uveal Tract	0	0	0	0	18	0	0	1,401	18	0	0	1,401
9. Vitreous Humor	13	0	0	841	18	1	1	1,909	31	1	1	2,750
10. Visual Cells and Pigment Epithelium	96	0	0	6,213	16	0	0	1,245	112	0	0	7,458
11. Retinal Organization and Visual Adaptation	63	0	0	4,079	14	0	0	1,090	77	0	0	5,169
12. Special Areas of Future Interest	2	0	0	130	19	0	6	2,564	21	0	6	2,694
Other*				2,433				1,798				4,231
TOTAL: *Retinal and Choroidal Diseases*	264	2	53	$23,125	236	15	20	$27,217	500	17	73	$50,342

*Core Centers, Research Career Awards, and Research Training

Note: The three project and resource tables are explained in the introduction to this volume.

Table 3: Recommendations by Subprogram

Chapter 1: Developmental and Hereditary Disorders

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. The Normal Retina (F)			
1. Continue intensive research on basic science of the retina (See Chapter 9 *Vitreous Humor* Chapter 10. *Visual Cells and Pigment Epithelium*, and Chapter 11 *Retinal Organization and Visual Adaptation*)	[41]	[5 projects 1]	
B. Development of Hereditary Retinal Degenerations			
1. Development of improved, noninvasive clinical diagnostic techniques (electrophysiologic, psychophysical, etc.) (CR)		3 projects 1	
2. Pathogenesis of hereditary retinal degenerations (F) (See also Chapter 10 *Visual Cells and Pigment Epithelium*)			
a. Tissue culture of retinal pigment epithelium	3	1 project	
b. Biochemical genetics	2	1 project	
c. Renewal, recognition, and phagocytosis of visual cells	2		
3. Tissue acquisition: special programs (RD)			
a. Animal models (mice, cats, dogs)	2	1	
(See Chapter 12 *Special Areas of Future Interest*)			
b. Donor eyes			[2]
c. Special sponsored research)			[1]
d. Clinicopathologic correlations		2 projects	
4. Biochemical abnormalities: second messenger — compare normal to heredity retinal degeneration (F) (See also Chapter 10, *Visual Cells and Pigment Epithelium*)	2		
5. Other related studies (F) (See also Chapter 10, *Visual Cells and Pigment Epithelium*, and Chapter 11 *Retinal Organization and Visual Adaptation*)			
a. Light effects	2		
b. Antigen studies	2		
c. Chromosome studies	1		
d. Anatomical studies of phagocytosis of shed photoreceptor outer segment discs	1		
e. Metabolic relationship of neurons and glial cells	1		
TOTAL *Developmental and Hereditary Disorders*	18	2 (including 7 projects)	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 20)	[41]	[1 (including 5 projects)]	[3]

Key
F — Fundamental Research
CR — Clinical Research
CT — Clinical Trial
RD — Resource Development
[ ] — Counted in another subprogram as noted

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Fundamental Studies			
1. Regional differences in anatomy and pathology (F)			
a. Structural differences in blood vessels in central and peripheral retina	2		
b. Blood vessels in tissue culture	2		
c. Blood vessel permeability (normal vs. disease)	2		
d. Effect of hypertension	1		
2. Physiological studies (F)			
a. Control of blood flow: effects of oxygen saturation, blood pressure, and metabolic state	1		
b. Mechanism of edema formation	1		
c. Capillary closure	1		
d. Large vessel closure	1		
e. Transport of sugars, amino acids, proteins, and water into and across neural retina in health and disease (See also Chapter 11, *Retinal Organization and Visual Adaptation*)	4		
3. Other special studies (F)			
a. Pigment epithelial permeability: effect of pharmacological agents	2		
b. Angiogenic substances, antagonists, and inhibitors	2		
c. Biochemical abnormalities of diabetic retinas (from donor eyes and animal models)	2		
d. Clotting mechanisms	1		
e. Normal metabolism of retinal blood vessels (See also Chapter 11, *Retinal Organization and Visual Adaptation*)	3		
f. Metabolic relationship of neurons and glial cells (See also Chapter 11, *Retinal Organization and Visual Adaptation*)	1		
g. Maintenance of retina under conditions of stress (See also Chapter 11, *Retinal Organization and Visual Adaptation*)	3		
B. Clinical (Natural History) Studies (CR)			
1. Diabetic retinopathy			
a. Neovascularization		1 project	
b. Edema		1 project	
c. Ischemia		1 project	
2. Branch vein occlusion		1 project	
3. Central vein occlusion		1 project	
4. Retrolental fibroplasia	1		
5. Sickle retinopathy		1 project	
6. Others, including cranial arteritis	1		
C. Design and Evaluation of Treatment (CT)			
1. Laser management			
a. Diabetes mellitus			
1) Retinal neovascularization		1 project	
2) Macular edema		2 projects	
3) Iris neovascularization			3
b. Branch vein occlusion		1 project	
c. Central vein occlusion		1 project	
d. Sickle retinopathy		1 project	
2. Retrolental fibroplasia	2		
TOTAL: *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*	33	3 (including 12 projects)	3

(Estimated Number of New Principal Investigators Required, FY 1978-80: 30)

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Normal and Abnormal Sclera and Vitreous Body (F)			
1. Myopic structure vs. normal	2		
2. Biochemistry (F)			
a. Scleral components	1		
b. Tissue culture	2		
3. Physiology (F)			
a. Scleral rigidity	2		
b. Psychophysics of retina in myopia	2		
B. Animals Models (F, RD)			
1. Eyelid closure	1		
2. Atropine effects	1		
3. Light effects	1		
4. Hereditary forms	1		
C. Clinical Research (CR)			
1. Natural history of myopia	2		
D. Treatment (CT)			
1. Atropine trial			3
TOTAL: *Myopia*	15	0	3
(Estimated Number of New Principal Investigators Required, FY 1978-80: 11)			

Recommendation	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Etiology (F)			
1. Role of reverse transcriptase		2 projects	
2. Search for a virus in ocular tumors	2		
3. Spontaneous animal model of retinoblastoma	1		
4. Establish animal models of retinoblastoma and melanoma	1		
B. Pathogenesis (F)			
1. Cells or origin of retinoblastoma and malignant melanoma		1 project	
2. Tumor angiogenesis factor		1 project	
3. Calcification and spontaneous regression	1	1	
4. Photoreceptor cell elements		1 project	
C. Histologic Studies (CR)			
1. Re-evaluate the classification of retinoblastoma		1 project	
2. Relation of size of tumor to cell type and prognosis		1 project	
3. Ocular tumor registry		1 project	
D. Diagnosis of Ocular Tumors (F, CR)			
1. ^{32}P for diagnosis (CT)		1 project	
2. a. HLA antigens		1 project	
b. Tumor-related circulating antibodies and cell-mediated sensitivity		1 project	
c. Skin test		1 project	
3. Paracentesis to search for melanin precursors in melanoma and isoenzymes of LDH in retinoblastoma	1		
4. Chromosome studies	1	1	
5. Tumor measurement techniques		1 project	
E. Treatment of Ocular Tumors (CR)			
1. Tumor registry	*		
2. Evaluate various methods of treating ocular tumors		2 projects	
3. Comparative study of X-ray therapy, photocoagulation, cryotherapy, and other surgical methods	1		
4. Evaluate immunologic status of spontaneously cured retinoblastoma and melanoma patients	1		
5. Evaluate BCG vaccine and DNCB in treating malignant melanoma	1		
6. Chemotherapy of retinoblastoma	1		
F. Epidemiologic Studies (CR)			
1. Incidence and frequency of various types of ocular tumors	1		
TOTAL: *Tumors*	12	2 (including 15 projects)	0

(Estimated Number of New Principal Investigators Required, FY 1978-80: 20)

*See Recommendation C. 3 above

Recommendations	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Anatomy (F, CR)			
1. Aging changes in neural retina, pigment epithelium, and choroid	2		
2. Maintenance of structural integrity: central vs. peripheral retina (See also Chapter 11, *Retinal Organization and Visual Adaptation*)	4		
B. Physiology (F, CR)			
1. Neural retina/pigment epithelium relationships: a. Control of photoreceptor shedding b. Protein transport across neural retina c. Blood-retinal barrier	5		
2. Choroidal circulation	1		
3. Psychophysical and electrophysiological studies of normal and diseased macula	2		
C. Biochemistry (F)			
1. Tissue culture of retinal pigment epithelium (See also Chapter 10, *Visual Cells and Pigment Epithelium*)	3		
2. Aging changes in normal retina, pigment epithelium, and choroid	3		
3. Angiogenesis factor	2		
4. Toxic susceptibility of the macula (See Chapter 12, *Special Areas of Future Interest*)	[2]		
D. Pathology (F)			
1. Photoreceptor renewal and phagocytosis	3		
E. Animal Models (F, RD)			
1. Identify existing animal models of macular disease (dogs with central progressive retinal atrophy, guinea pig, baboon)	1		
2. Develop new animal models	2		
F. Clinical Studies and Natural History (Combined with donor eye program) (CR)			
1. Senile macular degeneration	2	2 projects	
2. Central serous retinopathy		2 projects	
3. Hereditary macular degeneration			1
4. Case control study of risk factors			2
5. Toxic macular disease (See Chapter 12, *Special Areas of Future Interest*)	[2]	2	
6. Clinicopathologic correlations in human donor eyes and eyes from animal models (guinea pig, baboon)	3		
G. Treatment (CR, CT)			
1. Evaluate proposed treatments for senile macular degeneration		2 projects	
2. Evaluate current treatment of central serous retina		2 projects	
3. Search for treatment of hereditary macular degeneration (collect and evaluate experience, then conduct clinical trial)	2		
TOTAL: *Macular Diseases*	35	2 (including 8 projects each)	4
(Estimated Number of New Investigators Required, FY 1978-80: 20)	[4]		

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Diagnostic Techniques (F, CR)			
1. Research in optics			
a. Wide-angle ophthalmoscopy and photography		2 projects	
b. Monochromatic light studies		2 projects	2
c. Specular optics		2 projects 1	
d. Holography		2 projects	
2. Research in electrical and functional testing of the retina			
a. Electrical testing		1 project	
b. Functional testing — psychophysics		2 projects 1	
B. Pathogenesis (F, CR)			
1. Vitreoretinal osmotic relationships (See also Chapter 9, *Vitreous Humor*, and Chapter 11, *Retinal Organization and Visual Adaptation*)	4		
C. Other Fundamental Studies (F, CR)			
1. Retinochoroidal relationships			
a. Adhesions	2		
b. Osmotic relationships (See also Chapter 11, *Retinal Organization and Visual Adaptation*)	2		
2. Study of blood-retina barrier	2		
3. Maintenance of structural integrity: macula vs. periphery (See also Chapter 11, *Retinal Organization and Visual Adaptation*)	3		
D. Treatment (CR)			
1. Adhesive power of induced chorioretinal scars	1		
2. Better scleral implants	1		
3. Treatment of severe cases	1		
4. Improvement in vitreous surgery (See also Chapter 9, *Vitreous Humor*)	2		
E. Prevention (CT)			
1. Best method of prophylaxis		2 projects	
2. Selection of cases		2 projects 1	
3. Predisposing factors		3 projects	
4. Influence of circulatory deficiency		2 projects	
F. Animal Models (RD)			
1. Development of animal models	2		
TOTAL: *Retinal Detachment*	20	3 (including 20 projects)	2

(Estimated Number of New Principal Investigators Required, FY 1978-80: 34)

Chapter 7: Inflammatory Disorders

Recommendation	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Improved Diagnosis (CR)			
1. Develop improved methods for tissue biopsy			
a. Sampling of the vitreous		2 projects	
b. Chorioretinal biopsy			
B. Clinicopathologic Studies (F, CR, RD)		1	
1. Conduct clinicopathologic studies in uveitis		1 project	
2. Establish registry of uveitis patients			1
C. Animal Models (RD)			
1. Investigate experimental induction and treatment of inflammatory eye disease in animals	2		
a. Toxoplasmosis			
b. *Candida* endophthalmitis			
D. Immunology (F) (See also Chapter 8, *Uveal Tract*)			
1. Study mechanisms of immunogenic inflammation			
a. Antibody-complement mediated reaction	2		
b. Cellular immune reactions	2		
2. Study the uvea in systemic immunologic disease	1		
3. Investigate uveal auto-allergy			
a. Antigens of retina, lens, retinal pigment epithelium	1		
b. Sympathetic ophthalmia and Vogt-Koyanagi syndrome	1		
4. Determine nature of uveal response to infectious agents			
a. Viral	1		
b. Parasitic	1		
c. Bacterial	1		
E. Pathology (F)			
1. Effect of ocular inflammation on renewal, recognition, and phagocytosis of photoreceptor outer segments	2		
F. Biochemistry (F)			
1. Tissue culture of retinal pigment epithelium to investigate inflammatory diseases (See also Chapter 10, *Visual Cells and Pigment Epithelium*)	2		
G. Physiology (F)			
1. Tissue culture of neural retina to investigate inflammatory diseases (See also Chapter 11, *Retinal Organization and Visual Adaptation*)	2		
H. Treatment (CT)			
1. Conduct controlled, randomized trials of treatment regimens			
a. Toxoplasmosis		3 projects	1
b. Sarcoidosis			
c. Rheumatoid arthritis			
TOTAL: *Inflammatory Disorders*	18	2 (including 6 projects)	1

(Estimated Number of New Principal Investigators Required, FY 1978-80: 14)

Chapter 8: Uveal Tract

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Anatomy (F, CR)			
1. Compare central vs. peripheral choroid	2		
2. Investigate the effect of aging on the choroid and Bruch's membrane	1		
3. Undertake clinicopathologic correlations in donor eyes	2		
B. Physiology (F, CR)			
1. Study uveal hemodynamics			
a. Blood flow measurement	2		
b. Neural control	1		
c. Intraocular pressure	1		
d. Aging changes	1		
e. Osmotic relationships	2		
2. Search for an angiogenesis factor in uveal neovascularization	2		
C. Biochemistry (F)			
1. Culture uveal tissue			
a. Choroid	2		
b. Bruch's membrane	1		
c. Iris	1		
D. Immunology (F) (See Chapter 7, *Inflammatory Disorders*)			
1. Study mechanisms of immunogenic inflammation			
a. Antibody-complement mediated reactions	[2]		
b. Cellular immune reactions	[2]		
2. Study the uvea in systemic immunologic disease	[1]		
3. Investigate auto-allergy			
a. Antigens of retina, lens, retinal pigment epithelium	[1]		
b. Sympathetic ophthalmia and Vogt-Koyanagi syndrome	[1]		
4. Determine nature of uveal response to infectious agents			
a. Viral	[1]		
b. Bacterial	[1]		
c. Protozoan	[1]		
TOTAL: *Uveal Tract*	18	0	0
	[10]		
(Estimated Number of New Principal Investigators Required, FY 1978-80: 14)			

Recommendation	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Anatomy (F)			
1. Continue anatomical and morphological studies			
a. Cellular constituents	1		
b. Vitreous membranes (See also Chapter 6, *Retinal Detachment*)		1 project	
c. Gel regeneration	1		
d. Clinicopathologic correlations		2 projects	
e. Age changes	1		
B. Biochemistry and Metabolism (F)			
1. Modifications in physical state (See also Chapter 6, *Retinal Detachment*)	1		
2. Tissue culture			
a. Metabolism	1		
b. Age changes	1	1	
3. Interrelationships with other ocular tissues (retina, lens, ciliary body)	1		
C. Physiology (F)			
1. Immunology	1		
2. Permeability	1		
3. Vitreous scarring (See also Chapter 6, *Retinal Detachment*)		1 project	
4. Age changes	1		
5. Trauma	1		
D. Vitreous Substitutes (RD)			
1. Delineate needs and indications for vitreous substitutes		1 project	
E. Animal Models (RD)			
1. Animal models	1		
F. Treatment (CT)			
1. Study effects of antibiotics on vitreous and retina	2		
2. Improve techniques and instrumentation for vitreous surgery	2		
3. Other studies such as the collaborative Diabetic Retinopathy Vitrectomy Study	2		1
TOTAL: *Vitreous Humor*	18	1 (including 5 projects)	1

(Estimated Number of New Principal Investigators Required, FY 1978-80: 16)

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Physiology (F)			
1. Photoreceptor membrane development	2		
2. Renewal of photoreceptors	3		
3. Interactions between photoreceptors and pigment epithelium (See also Chapter 1, *Developmental and Hereditary Disorders*, Chapter 5, *Macular Diseases*, and Chapter 7, *Inflammatory Diseases*)	3 [9]		
4. Photoreceptor capacity in advanced retinal degeneration	2		
B. Biochemistry (F)			
1. Membrane properties of photoreceptors and pigment epithelium	3		
2. Control of photoreceptor and pigment epithelium properties by calcium, cyclic nucleotides, hormones, and other cell products	1		
3. Effect of light and nutrition on photoreceptor and pigment epithelium metabolism (See also Chapter 1, *Developmental and Hereditary Disorders*)	2 [2]		
4. Second messengers: compare normal to hereditary retinal degeneration and macular degeneration (See Chapter 1, *Developmental and Hereditary Disorders*)	[2]		
5. Tissue culture of retinal pigment epithelium (See Chapter 1, *Developmental and Hereditary Disorders*, Chapter 5, *Macular Diseases*, Chapter 7, *Inflammatory Disorders*, and Chapter 12, *Special Areas of Future Interest*)	[9]		
6. Transport to photoreceptors (vitamin A, etc.) (See Chapter 12, *Special Areas of Future Interest*)	[2]		
D. Animal Models (RD)			
1. Find specific faults which determine manifestations of retinal diseases (See Chapter 1, *Developmental and Hereditary Disorders*, Chapter 5, *Macular Diseases*, Chapter 7, *Inflammatory Disorders*, and Chapter 7, *Inflammatory Disorders*) (For related discussion, also see Chapter 12, *Special Areas of Future Interest*)	[7]		[3]
TOTAL: *Visual Cells and Pigment Epithelium*	16	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 10)	[31]		[3]

Note: All projects listed under Chapter 10, Visual Cells and Pigment Epithelium, *and Chapter 11,* Retinal Organization and Visual Adaptation, *require basic science skills for their accomplishment. However, many of these projects, although identified under these basic programs, have been assigned to and are counted in clinical subprograms to emphasize the relevance of such basic information to the solution of major disease problems. Indeed, without such knowledge, there truly can be no clinical research.*

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Anatomy (F)			
1. Identification of specific connections of retinal neurons	1		
2. Maintenance of structural integrity: macula vs. periphery (See Chapter 5, *Macular Diseases*, and Chapter 6, *Retinal Detachment*)	[7]		
3. Anatomical correlates of visual excitation in vertebrates and invertebrates	2		
4. Histochemistry: localization of enzymes and neurotransmitters	2		
B. Physiology (F)			
1. Intracellular recordings from mammalian retinas	3		
2. Maintain retina in altered environments	3		
(See also Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*, and Chapter 7, *Inflammatory Disorders*)	[2]		
3. Protein transport into and across neural retina (See Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*, and Chapter 5, *Macular Diseases*)	[9]		
4. Vitreoretinal osmotic relationships (See Chapter 6, *Retinal Detachment*)	[4]		
5. Retinochoroidal osmotic relationships (See Chapter 6, *Retinal Detachment*)	[2]		
C. Biochemistry (F)			
1. Nutrition of retinal blood vessels (See Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*)	[3]		
2. Metabolic relationship of neurons and glial cells (See Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*)	[1]		
D. Neuropharmacology (F)			
1. Identify specific receptors	1		
2. Characterize physiological responses to individual neurotransmitters	2		
E. Experimental Pathology (F)			
1. Maintenance of retina in vivo under conditions of stress (See Chapter 2, *Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities*)	[3]		
TOTAL: *Retinal Organization and Visual Adaptation*	14	0	0
	[31]		
(Estimated Number of New Principal Investigators Required, FY 1978-80: 8)			

Note: All projects listed under Chapter 10, Visual Cells and Pigment Epithelium, *and Chapter 11,* Retinal Organization and Visual Adaptation, *require basic science skills for their accomplishment. However, many of these projects, although identified under these basic programs, have been assigned to and are counted in clinical subprograms to emphasize the relevance of such basic information to the solution of major disease problems. Indeed, without such knowledge, there truly can be no clinical research.*

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Toxic and Environmental Disorders (F)			
1. Determination of safe levels of light and other forms of radiation	2		
2. Toxic effects on the developing retina and on the macula (drugs, diet, oxygen, carbon monoxide)	2		
3. Clinical significance of drug-related changes	2		
4. Determine mechanisms of drug penetration into the eye	2		
5. Transport to photoreceptors (vitamin A, etc.) (See also Chapter 10, *Visual Cells and Pigment Epithelium*)	2		
B. Low Vision (CR)			
1. Use of bright light, contrast, color, and magnification to improve visual acuity	1		
2. Improved use of peripheral retina	1		
3. Evaluation of laser-generated images	2		
C. Retinal Regeneration and Transplantation (F)			
1. Optic nerve degeneration and regeneration	2		
2. Regeneration of neural retina and its embryological development	2		
3. Tissue culture of retinal pigment epithelium (See also Chapter 10, *Visual Cells and Pigment Epithelium*)	1		
D. Tissue Acquisition and Distribution (RD)			
1. Human donor eyes and animal models (See also Chapter 1, *Developmental and Hereditary Disorders*, and Chapter 10, *Visual Cells and Pigment Epithelium*)			6
TOTAL: *Special Areas of Future Interest*	19	0	6
(Estimated Number of New Principal Investigators Required, FY 1978-80: 11)			

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Corneal Diseases

Overleaf: *Recurrent human herpes simplex infection of the cornea with multiple large dendritic ulcers.*

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Foreword

IN PREPARING THIS report, the *Corneal Diseases* Panel of the National Advisory Eye Council's Program Planning Subcommittee sought representation and ideas from a broad segment of the vision research community including scientists from the major geographic areas of the United States and from a variety of disciplines which might be involved in research on corneal and adnexal diseases. The Panel and several consultants assembled at the National Institutes of Health in Bethesda, Maryland, for a two-day meeting to define research needs and opportunities and to assign priorities within corneal and adnexal research in terms of the national interest. In the course of its deliberations, the Panel examined the wide range of corneal, lid, conjunctival, lacrimal, orbital, and external ocular diseases; corneal refractive errors and injuries; drug delivery; corneal transplantation; and the use of contact lenses for both optical and therapeutic purposes.

In the following pages, the *Corneal Diseases* Panel has identified several priority areas of research. These are generally based on the morbidity and clinical importance of the problem, disorder, or disease; the likelihood that reasonable investments of ideas, money, and manpower will yield valuable information in a relatively short period of time; and the belief that corneal research can provide unique opportunities to clarify important problems in general medicine. Examples are the treatment of viral disease and development of antiviral drugs, the study of the immunopathology of disease, and therapeutic approaches to transplantation immunity in this highly accessible tissue. The development of antibiotics and newer radiological techniques are also considered important research needs but are areas in which industry and other branches of science have made major contributions in the past and are expected to do so in the future without specific initiative by the National Eye Institute.

Introduction

THE CORNEA IS the clear transparent structure at the front of the eye that, by means of its convex surface, acts as a powerful lens. The cornea contains no blood vessels but is completely nourished by the fluids that bathe it and the limbal vessels. Almost twice as thick at its periphery as it is at its center, the cornea can be divided into five layers: the epithelium, Bowman's membrane, the stroma, Descemet's membrane, and the endothelium. Although the epithelium has the power to regenerate and heal rapidly without scarring, injury to the deeper corneal structures usually results in the formation of an opacity.

The National Eye Institute's *Corneal Diseases* research program includes corneal, lid, conjunctival, and lacrimal system disorders, orbital and external ocular diseases, and corneal refractive errors and injuries. The *Corneal Diseases* Panel has established the following six subprograms encompassing these general topics:

1. External Ocular Infections and Inflammatory Diseases
2. Dry Eyes and Tear Abnormalities, Epithelial Disorders, and Drug Delivery
3. Refractive Problems and Contact Lenses
4. Corneal Edema, Dystrophies, and Inherited Disorders
5. Corneal Transplantation and Stromal Injury and Repair
6. Tumors and Other Lid, Conjunctival, and Orbital Problems

Such disorders, diseases, and injuries may produce impaired vision, unilateral loss of sight, or bilateral blindness. They all offer a wealth of opportunity for productive research.

Importance

Over 2 million cases of corneal disorders and diseases occur each year in the United States, and over 1.7 million injuries to the cornea and its adnexa are also recorded.* These account for 62 percent of the total incidence of all acute and

*Except where specifically referenced, incidence, prevalence, and cost statistics quoted in this report can be found in or have been derived from: Westat, Inc, *Summary and Critique of Available Data on the Prevalence and Economic and Social Costs of Visual Disorders and Disabilities*, Rockville, Maryland, 16 February 1976.

chronic disorders, diseases, and injuries to the eye. Every year these conditions account for over 100,000 hospital days and for over $12 million in surgical costs alone. Corneal problems other than refractive errors necessitate approximately 10 million annual office visits for professional eye care; this is one-third of all visits for professional eye treatment or care.

Disorders which require only optical correction are also important. Virtually everyone over the age of 45 needs some means of optical correction, and it is estimated that 100 million people wear corrective lenses for which as much as $1.8 billion is spent annually. Additionally, 300,000 people a year require special corrective lenses following cataract extraction. Every year there are 9 million visits to ophthalmologists for refractive errors, accounting for 30 percent of all visits to these physicians. Additionally, there are estimated to be over 25 million visits annually to optometrists, the majority of which are for correction of refractive errors.

The causes of corneal diseases include bacterial, fungal, and viral infections, allergic reaction, improper moistening and covering of the cornea by the eyelids, birth defects, and degenerative conditions.

The prevalence of legal blindness from corneal diseases, which is about 6 percent of all legal blindness, is not high in comparison to that from other eye disorders. Nevertheless, corneal and external eye disorders and diseases cause severe disability and pain and require a considerable amount of physician care. Ocular infections and allergies (most of which are conjunctival) and ocular injuries (most of which are from foreign bodies or traumatic injuries involving the cornea) are the most common eye problems.

Accomplishments

Advances in corneal disease research hold great potential for improving the ability of millions of Americans to cope with infections, disorders, diseases, and injuries of this important ocular tissue.

Corneal disease caused by bacterial infection can often be treated with antibiotics, and there has been some success in treating corneal disease caused by viruses. Idoxuridine (IDU), developed in the early 1960's for treating herpes simplex infection of the cornea, was the first drug proved useful in treating any human viral disease. A new antiherpes drug, vidarabine, is expected to be valuable for treating patients who either do not respond to IDU or in whom that drug produces undesirable side effects. The antifungal drug, pimaricin, the testing of which was supported by the NEI, is now the drug of choice for fungal keratitis.

An important new approach to drug delivery and for treating dry eyes consists of placing ocular inserts under the eyelid where they slowly and systematically melt, providing the eye with needed moisture or medication. Other inserts that do not melt can deliver drugs at precisely controlled rates.

When corneal diseases or injuries are not treated promptly—or despite treatment—the cornea may become scarred or opaque, blocking the passage of light and resulting in impaired vision or blindness. In such cases, a corneal transplant, replacement of the diseased tissue with a healthy cornea from the eye of a donor postmortem, may be able to restore sight. Corneal transplantation is one of the most successful of all tissue transplant operations; its overall success rate has improved more than 50 percent over the last decade. At this time, 85 percent of all corneal transplants remain clear.

Until recently, short-lived refrigerated tissue was essential for most corneal transplant operations. Now, two procedures permit the storage of donated

corneas from a period of days to months or years. For short-term storage of up to seven days, a nutritive liquid called M-K media may be used to keep the corneal tissue fresh and viable at a temperature of 4 degrees Centigrade. Cryopreservation, in which corneas are frozen by reducing the temperature at a precisely controlled rate to minus 190 degrees Fahrenheit, may be employed to preserve corneal tissue for an indefinite period of time.

Studies of the structural basis for corneal transparency have provided considerable information on how the cornea normally maintains its clarity and how injury or disease may disrupt this process. Enzymes are produced which cause corneal melting, and these could be inactivated. A modified specular microscope, which permits viewing the endothelial cells in the intact human eye, has greatly advanced the clinical study of the growth, development, and healing of intact corneal cells.

Research on soft contact lenses has demonstrated that these devices can act as a protective dressing or bandage which eases pain and promotes healing in a variety of corneal diseases.

Recent research into other types of contact lenses offers exciting new possibilities for correcting optical defects. These may be important to the estimated 8 million people already wearing either hard or soft contact lenses in this country and will almost certainly improve the optical correction of postcataract and corneal disease patients. Research to optimize optical correction and to minimize the possibility of eye damage from contact lens wear is an extremely important area for future research. Experiments with extended-wear or continuous-wear contact lenses are beginning; the groundwork for such devices has already been laid by basic studies. It is possible that such lenses may one day render the wearing of eyeglasses obsolete.

These and other future contributions of corneal research will undoubtedly make a significant contribution to the American economy and quality of life.

Goals of Corneal Diseases Research

- Understand normal corneal development, structure, and metabolism
- Understand how disruption of normal processes by prenatal or developmental influences, external factors, or other eye or systemic disorders can lead to corneal disease
- Discover means to prevent corneal diseases
- Treat these diseases effectively once they occur
- Improve the early diagnosis of corneal diseases and classify them more accurately
- Define with sufficient clarity those corneal diseases which are hereditary in nature in order to make rational genetic counselling possible
- Develop effective methods of restoring visual function lost as a result of corneal diseases

Summary of Recommendations

IN THIS REPORT, the *Corneal Diseases* Panel has attempted to identify several high priority areas for research in this field. As noted in the Foreword, these priorities are based on the importance of the afflictions to mankind, the likelihood that reasonable investments of time and money will yield valuable information, and the belief that in certain areas eye disease provides a unique opportunity to clarify important systemic problems and make contributions which will be of wide benefit to all medicine.

The following is a short summary of the most important recommendations made by the Panel for future corneal and adnexal disease research. Each of these is discussed in detail in subsequent sections of this report.

1. *Herpes Simplex*—Investigate the roles of live herpes virus and its antigenic products, the host inflammatory responses to herpes infection, and the neuronal factors responsible for viral latency and reactivation, and develop effective antiviral therapy.

2. *Dry Eyes and Tear Abnormalities*—Determine the composition and biophysical characterization of tears, study tear flow and drainage problems, describe the immune mechanism in lacrimal gland dysfunction, improve the clinical diagnosis of tear-deficient states, and study blink mechanisms and blink stimulation.

3. *Ephithelial Disorders and Surface Injuries*—Study the adhesion between the epithelium and its underlying tissue, search for epithelial growth stimulators, improve treatment of the chronically inflamed epithelium, and prevent destruction of the stroma by epithelial opacity and vascularization.

4. *Drug Delivery*—Develop and evaluate new means of drug delivery, study the pharmacokinetics of ocular drugs, and determine genetic influences on drug reactions.

5. *Continuous-Wear Contact Lenses and New Contact Lens Materials*—Determine the effects of new contact lens materials upon corneal physiology and metabolism, and establish criteria for the safety, efficacy, and uses of new lens materials.

6. *Orthokeratology*—Establish the extent and duration of correction obtained by orthokeratology and the risks involved in this procedure.

7. *Corneal Edema, Dystrophies, and Inherited Disorders*—Determine endothelial regeneration capacity, the effects of different surgical procedures and drugs upon the endothelium, the characteristics of endothelial diseases, and the best methods of corneal preservation.

8. *Corneal Transplantation*—Improve specular microscopy and the M-K media, perform a study of blocking antibodies before corneal transplantation, investigate transplantation antigens, determine the source of collagenolytic enzymes, their biochemical properties, and pharmacological inhibitors, and study the use of angiogenesis inhibitors to prevent corneal vascularization. Investigate means of improving the outcome of corneal transplantation by applying modern immunological techniques.

9. *Corneal Stromal Injury and Repair*—Investigate the characteristics of the structural macromolecules of the normal and scarred cornea and their effects upon vision and find pharmacological means of manipulating the biosynthetic and degradative pathways of corneal metabolism to prevent or reverse scarring.

10. *Tumors and Other Lid, Conjunctival, and Orbital Problems*—Establish diagnostic protocols for patients with orbital lymphoma, and determine the role of environmental factors in the etiology of basal cell carcinoma of the eyelids.

1

External Ocular Infections and Inflammatory Diseases

THE CORNEAL DISEASES PANEL, in consultation with leading experts in external ocular infection and inflammation, has selected Herpes Simplex as the area of highest research priority within this subprogram.

Herpes Simplex

Herpes simplex keratitis, which is the most common severe ocular infection in the United States, has an estimated incidence of 297,000 annual cases. See Figure 1. The disease typically begins during childhood or adolescence and frequently recurs, causing severe disability and major loss in productivity. It is a growing nemesis, especially among patients with primary or medically-induced immunological incompetence. Medical therapy requires frequent return visits to the physician over periods ranging from one week to several months. Approximately 50 percent of those who develop herpes simplex epithelial keratitis are likely to experience recurrence of epithelial disease or a complication of deep stromal keratitis or uveitis within two years.[1]

Herpes infection of the corneal stroma frequently produces irreversible structural alteration of the cornea. Special straining with hybrid antibodies and immunoelectron microscopy studies show that once a cell has been infected by herpes, its cell membrane is altered. In Figure 2, viral antigen (arrows) is incorporated into the cell membrane. The cell is now different from normal cells and capable of a severe destructive immune reaction even without virus being produced. Herpes simplex often results in monocular blindness, a fact not reflected by available morbidity data. Corneal transplantation (keratoplasty) remains the only satisfactory method for restoring vision to a large percentage of these patients, but the benefits from this treatment may be reversed by recurrence of active viral replication or inflammation. Type II *herpesvirus hominus* infection of the maternal reproductive system produces neonatal infection in an estimated 1 in 7,000 births, a condition characterized by disseminated skin eruption, conjunctival and corneal infection, central nervous system disease, and a fatality rate of 50 percent.[2]

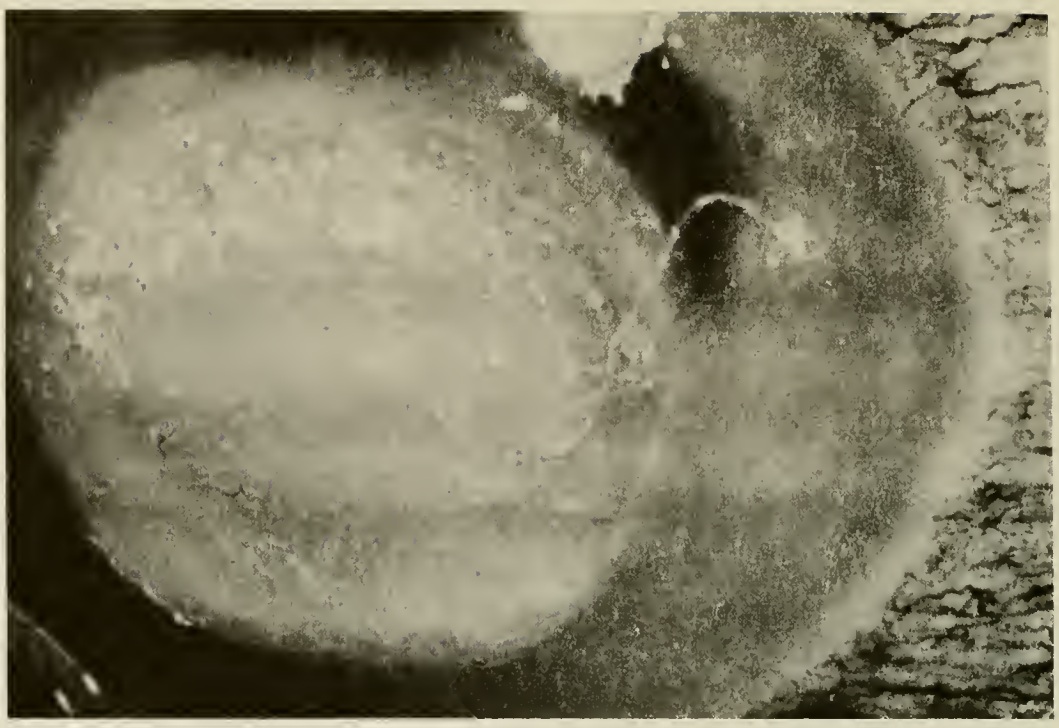

Figure 1. Corneal ulcer and vascularization caused by herpes simplex virus.

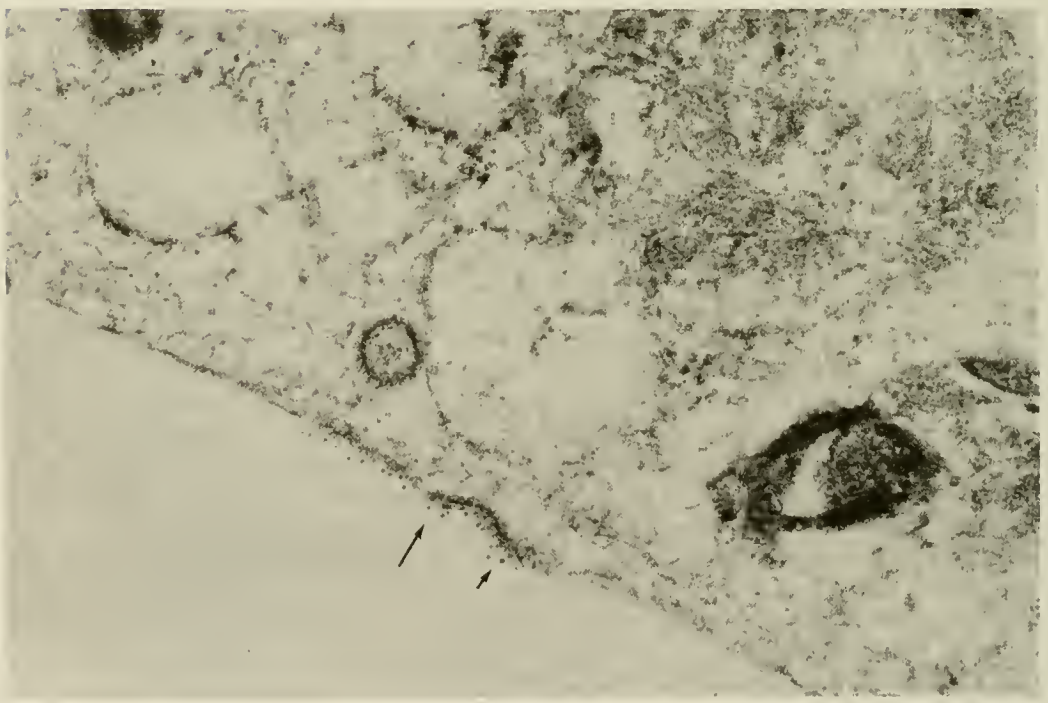

Figure 2. Herpes virus infection of a corneal cell.

In addition to the recognized forms of ocular involvement in primary and recurrent infection, herpes simplex may be responsible for a large portion of cases of idiopathic stromal keratitis, uveitis, secondary glaucoma, and retinitis. By altering corneal structure and the inflammatory response, herpes keratitis predisposes the host to a variety of severe complications including secondary microbial infection, permanent endothelial dysfunction, cataract, secondary glaucoma, and intolerance to visual devices.

The eye has served and continues to serve as the best model for elucidating the pathogenesis of herpes simplex infection and for developing effective methods for its prevention and cure. The antiviral drugs now being tested in the treatment of generalized herpetic viral disease were originally tested and proven in the eye. The possible therapeutic use of interferon, the mechanism of host defense, and viral latency and recurrence are best studied in the eye. Knowledge derived from such studies will provide a valuable key to understanding herpes simplex infection of the skin, central nervous system, motor nerves, and genitourinary tract, and probably most important, to understanding the possible relationship of herpes virus to cancer of the cervix and other organs. The products of this research may thereby be of great value to other medical disciplines.

Accomplishments

Vision research scientists have made landmark advances in the study of herpes simplex and its treatment. The introduction of idoxuridine for the therapy of ocular herpes simplex in 1962 represented the first successful application of a drug in the control of human viral disease and stimulated extensive effort toward development of other antiviral agents.[3] In fact, most of the new antiviral drugs now being studied for the treatment of systemic DNA virus diseases are tested early in their development against ocular disease. Basic and clinical investigations have established the value of idoxuridine, vidarabine, and trifluorothymidine in treating herpes simplex epithelial keratitis, thereby reducing the morbidity of the disease and hastening the return of the patient to a normal and productive life.

Immune responses to herpes virus have been found to play a major part in the production of severely necrotizing corneal stromal disease.[4,5] Although the exact mechanism by which this occurs is still not known, immunosuppressive drugs, such as corticosteroids, have been used with some success to treat this condition. The addition of antiviral drugs to the corticosteroid regimen has limited the possible enhancement of viral replication and has made the treatment much safer. Unfortunately, this treatment, although helpful, remains poorly understood. This is a problem not only for the treatment of ocular herpes disease but for the treatment of herpes infections at other sites.

The damage produced after viral infection may be caused primarily by host hypersensitivity to the virus. The development of better treatments for this hypersensitive response, whether in an annoying lip or genital herpes lesion or in potentially lethal encephalitis, may be clarified by further studies of the cornea. With its absence of blood vessels and relatively simple cellular patterns, the cornea can be cultured and studied more easily than most other tissues. Thus, ophthalmic investigators have a unique opportunity not only to prevent disabling eye disease but to develop findings which are of enormous importance to medicine as a whole.

Once someone has been infected by herpes, the risk of reinfection is approximately 50 percent within two years and greater if the observation period is extended. Investigators have determined that the trigeminal ganglion, and perhaps other ganglia around the eye, may be a source of this reinfection.[6] Virus

also is shed in tears, just as it is in saliva,[7] but the interrelationships between the virus shedding and the source remain unknown. If the biology of recurrent herpes can be understood in the eye, this would very likely lead to the elimination of recurrent cold sores and fever blisters, and perhaps to the eradication of herpes zoster and other recurrent viral diseases. It might even be of benefit in the possible link of genital herpes to cervical carcinoma.

Research Objectives

- Define the roles of herpes simplex virus and of the host factors in primary and recurrent infections of the cornea and in secondary herpetic uveitis
- Investigate neuronal factors responsible for recurrent herpes keratitis
- Find better means of treating herpes infections of the cornea, particularly deep-seated, stromal, and recurrent infections

Research Needs and Approaches

At present, there are very few research groups investigating herpes simplex infections of the eye. An analysis of NEI funding shows that ocular herpes research is being conducted by five modest-sized groups consisting of a total of about four clinical scientists and six or seven basic scientists.

One of the greatest research needs in this subprogram is to define the role of live herpes simplex virus, viral antigen and cell products, and the host inflammatory response in the production of secondary herpetic uveitis. Definition of these roles can only be provided through the combined efforts of immunologists, cell biologists, and virologists working with electron microscopists or morphologists and clinical investigators. The impact and yield of such information is expected to be considerable.

There is also need to define the host factors responsible for initial acquisition of the herpes simplex virus, for expression of the primary clinical infection, and for recurrence of this disease. This would require a multidiscipline, multicenter, prospective study with a duration of three to five years. Emphasis should be on the genetic and immunological factors related to the variable expression of the disease. The diverse manpower required would include virologists, epidemiologists, geneticists, immunologists, and clinicians.

Definition of the neuronal factors responsible for viral latency and reactivation is also important. Studies are needed to determine the pathways by which the virus reacts with the ganglia, the modes of interaction with the ganglia, and the trigger mechanisms for virus shedding. The existence of a rabbit model will facilitate these efforts. Accomplishment of these ends will require virologists, cell biologists, biochemists, immunologists, and experimental pathologists.

The ability of ophthalmic surgeons to cope with superficial epithelial ulceration has not solved the problem of herpes simplex because necrotizing, blinding stromal diseases that tend to be chronic still develop in a significant portion of patients. There is a high risk that patients who have once had ocular herpes will have repeated attacks throughout their lifetimes which will result in serious morbidity and often in blindness.[8]

It is likely that if recurrences of ocular herpes can be eliminated, perhaps through an understanding of its inciting factors, not only the management of ocular disease but of labial herpes, genital herpes, and perhaps even cervical carcinoma would be similarly benefited.

Another important research need is to develop more effective methods of treating ocular herpes simplex. There are many possible approaches to potential control of the agent and the disease process. One is to eliminate the virus from the target organ. Research to develop safer and more effective antiviral agents capable of reaching the site of virus replication by multiple routes of administration is needed. This search should extend beyond the present area of antimetabolites, and success in this area will require both individual effort and that of teams. The yield from such studies could be great and have direct applicability to the treatment of cutaneous, central nervous system, and genitourinary herpes infections.

Another method of controlling herpes simplex is to prevent transmission of the virus between hosts. But, because it is not likely that an effective vaccine can be developed, it is doubtful that this area offers major opportunity at this time.

Preventing spread of the virus to the neuronal reservoir is a third potential way to control the disease. Despite the potential significance of controlling the disease in such a way, investigative tools for accomplishing this do not yet exist.

Elimination of the virus from the neuronal reservoir and prevention of its release from the ganglion is a fourth possible method of control. Studies employing the animal model of latent infection and longitudinal clinical studies by virologists, cell biologists, immunopathologists, and clinical investigators are approaches to this method of therapy. In addition, important clues have been provided by studies using interferon. Teams of investigators should be organized to carry the work from the laboratory through to extensive clinical investigation.

A fifth possible method of controlling herpes simplex is to modify the host response. Investigators should attempt to develop methods of retaining the benefits of neuronal and cell-mediated immunity while preventing the harmful sequelae of the inflammatory response. There is a desperate need for anti-inflammatory agents which do not enhance viral replication. The expected yield from such investigations would be considerable, but the time requirement might be relatively long, perhaps seven to ten years. Manpower needs include immunologists, pharmacologists, and clinicians.

Priorities and Recommendations

- Determine the roles of live herpes simplex virus and its antigenic products
- Determine the host inflammatory response to herpes simplex viral infection and determine those host factors responsible for its recurrence
- Determine the neuronal factors responsible for viral latency and reactivation, the pathways of viral transmission for interaction with ganglia, and the mechanisms which trigger viral shedding
- Develop effective methods of herpes simplex viral therapy through elimination of the virus from its target organ and the neuronal reservoir by use of agents administered by multiple routes
- Modify host response by understanding neuronal and cell-mediated immunity and by preventing harmful sequelae of inflammation

Resource Requirements

The estimated fiscal year 1977 funding for *External Ocular Infections and Inflammatory Diseases* is $2,413,000. Additional projects in Herpes Simplex recommended by the Panel include 18 research grants and one specialized clinical research center grant at a total cost of $4,116,000 for FY 1978. The tables at the end of this report provide further details.

Other Important Research Areas

The *Corneal Diseases* Panel with its consultants judged that research in the following areas within this subprogram, though important, is of lesser priority, according to the criteria discussed in the Foreword to this report.

Herpes Zoster

Despite the low incidence and prevalence of ocular herpes zoster, this disease, which predominantly attacks middle-aged adults, forces loss of work and frequent, extended hospitalization. Common complications are secondary microbial infection, chronic epithelial and stromal ulceration, recurrent stromal keratitis, uveitis, and cataract. In addition, postherpetic neuralgia prolongs requirements for medical care and causes reduced visual function and suffering. Among the elderly, dissemination of infection may lead to severe central nervous system complications and death. Lid abnormalities, tear dysfunction states, and epithelial dysfunction in ocular herpes zoster limit the success of keratoplasty as a mode of therapy.

Adenovirus and Enterovirus

Adenovirus, which is the most frequent cause of epidemic ocular disease, predominantly attacks adults—thereby producing significant loss of productive time—and accounts for a large number of physician office visits. Epidemic outbreaks of this disease disrupt places of work, educational institutions, and recreational facilities. The ocular route of infection may lead to diseases in other organs, and disseminated infection in children can produce death. Adenovirus type 12 has been shown to produce cancer in laboratory animals, and enterovirus has caused epidemics of hemorrhagic conjunctivitis around the world.

Chlamydia

Although rare in the United States, the chlamydial infection trachoma is a leading cause of blindness throughout the world. Recent studies have defined the differences among subgroups of chlamydia and their relationships to endemic trachoma and paratrachoma (conjunctivitis of the newborn, inclusion conjunctivitis, and TRIC keratoconjunctivitis). Despite the containment of trachoma within restricted, small population groups in this country, chlamydial conjunctivitis is widespread among the young because of increasing chlamydial venereal disease which is easily spread to the eyes. This particular form of the disease does not produce significant ultrastructural or visual loss; however, its morbidity is relatively high because the disease fails to respond to conventional antimicrobial therapy. Also, due to the limited application of available diagnostic techniques, the infection may remain undetected for several weeks. Chlamydia is the most

common cause of nongonococcal urethritis in this country and may produce significant complications within the genitourinary tract. Understanding the epidemiology, pathogenesis, and treatment of the sexually transmitted form of chlamydial ocular disease may have direct application to the control of worldwide trachoma.

Bacterial and Fungal Keratitis

Bacterial and fungal infections of the cornea produce several structural alterations which frequently lead to blindness. Although the incidence of bacterial and fungal keratitis is low, the morbidity of such disorders is extraordinarily high: patients often require prolonged hospitalization and numerous physician visits over extended periods. These infections can be brought on by such causes as simple injury or contact lens abrasion. Patients whose corneal structure has been altered by other disease processes or who have immunological incompetence are particularly susceptible to these infections.

Idiopathic, Peripheral, Infiltrative, and Ulcerative Keratitis

Inflammation of the peripheral cornea may result from a variety of other diseases affecting the lids, conjunctiva, general immune system, and collagen-vascular system. Inflammations such as idiopathic, peripheral, infiltrative, and ulcerative keratitis may lead to severe alteration of the corneal structure, corneal perforation, and even blindness. Research on these corneal problems, such as that involving HLA typing and the search for autoimmune processes, may have relevance to many areas of medicine.

Allergic Diseases of the Conjunctiva and Cornea

Allergic diseases of the conjunctiva and cornea include contact allergy, hayfever conjunctivitis, vernal conjunctivitis, and atopic keratoconjunctivitis. Although the incidence of visual impairment due to contact allergy and hayfever conjunctivitis is low, these entities account for a great number of physician visits and large annual health care expenditures. Vernal conjunctivitis and atopic keratoconjunctivitis may produce severely altered corneal structures and render the victim susceptible to complications of medical therapy, such as those produced by corticosteroids. These complications may be devastating, particularly to the young.

Blepharokeratoconjunctivitis

Bacterial infection and sebaceous dysfunction of the lids are among the most common disorders encountered by the ophthalmologist. The frequency and chronicity of conditions such as blepharokeratoconjunctivitis account for sizable annual health care expenditures. Complications of these entities include malposition of the lids, meibomitis, hordeola, chalazia, erosion of the corneal epithelium, and a variety of peripheral corneal inflammations.

Accomplishments

Herpes Zoster

Although evidence links the role of circulatory varicella-zoster antibodies and the development of herpes zoster, the precise pathways for transmission of the

virus to the target site have not been established. Clinical investigation has substantiated the value of intravenous vidarabine in the control of cutaneous eruptions,[9] yet, no antiviral agent has proved successful in preventing the occurrence or reducing the severity of ocular complications. Research has established that inflammation is involved both in the primary response to the virus and in the recurrent infection, thereby supporting the value of corticosteroids in controlling the ocular effects. An animal model would facilitate research on the etiology of herpes zoster.

Adenovirus and Enterovirus

Serological studies have shown that the risk of adenovirus infection in this country is related to low levels of protective antibodies. It is now recognized that many types of adenovirus may produce a similar type of ocular disease, a concept further expanded by the identification of adenovirus type 19 as an ocular pathogen[10] and the isolation of an agent of acute hemorrhagic conjunctivitis.[11] New applications of group antisera and immunofluorescent antibody techniques have provided a rapid method of laboratory confirmation of adenoviral conjunctivitis,[12] an entity which can be clinically confused with herpes simplex and chlamydial conjunctivitis. There is no effective agent for preventing transmission of the disease or progression of ocular sequelae. Clinical investigations have substantiated that topical corticosteroids may indeed suppress the late corneal complication of adenoviral infection;[13] however, other therapeutic approaches are limited, and there is no animal model of adenoviral disease.

Chlamydia

Investigators have determined the ecological, socioeconomic, and host factors responsible for the varied expression of disease by subgroups of this agent.[14] Improved methods of laboratory diagnosis have resulted from extensive field trials and other clinical studies. Animal models now make it possible to examine the host response to the agent and to evaluate new antimicrobial agents.[15] The effectiveness of tetracycline and the value of controlling other host factors in reducing the morbidity of trachoma have been established by collaborative clinical studies.[16–18] There still, however, is no effective and practical method of immunization.

Bacterial and Fungal Keratitis

The simplicity and reliability of laboratory diagnosis of bacterial and fungal keratitis have been established. The development of animal models of these diseases has facilitated the introduction of new antimicrobial agents, especially the new drug of choice for fungal keratitis, pimaricin. They have also helped establish the separate roles of the organism itself and of the host inflammatory response in causing destruction of the stroma. Investigations have defined the significance of exotoxins and other microbial products in the total disease process and stimulated unique approaches to therapy. Enzymes produced by the pseudomonas organism can digest the cornea and cause perforation of the eye.

Idiopathic, Peripheral, Infiltrative, and Ulcerative Keratitis

Few accomplishments have been made within the past several years toward understanding the pathogenesis and therapy of these diseases. Nevertheless, investigators have suggested that alteration in limbal vasculature, release of

endogenous collagenase and protease, and abnormalities of host immune mechanisms may play important roles in these entities.[19,20]

Allergic Diseases of the Conjunctiva and Cornea

Recent accomplishments in this area include the definition of the role of IgE as a mediator of the allergic response, the development of human models of allergic disease, and the assessment of modifiers of the mastcell response pathways as potential therapeutic agents.

Blepharokeratoconjunctivitis

Although the role of staphylococcus has been defined in a portion of cases of blepharokeratoconjunctivitis, there has been little progress toward understanding the entire complexity of these diseases. It does appear that bacteria in the meibomian glands may break down fatty secretions to produce irritating toxic fatty acids. Low doses of tetracycline have shown some promise of providing relief.

Research Objectives

- Distinguish between the roles of replicating herpes zoster virus and the host response in ocular disease
- Develop improved antiviral and anti-inflammatory therapy for herpes zoster
- Develop better methods of diagnosing and means of preventing chlamydia
- Elucidate the pathogenesis of bacterial and fungal keratitis and blepharokeratoconjunctivitis
- Define multiple pathways of peripheral nonmicrobial corneal inflammation
- Develop effective methods of preventing and managing allergic diseases of the cornea and conjunctiva

Research Needs and Approaches

Herpes Zoster

One of the most important research needs for treating or preventing herpes zoster is the development of an animal model of this infection. Accomplishments by investigators of herpes simplex may have direct application to the development of an animal model of herpes zoster. The data expected to result from studies using this model would, as is the case in investigations of all ocular viral disease, likely be of considerable value to many areas of medicine.

Another research need for herpes zoster is to define the role of the virus in ocular disease. These investigations should distinguish between the role of the replicating virus and that of the host response in adnexal, conjunctival, corneal epithelial, stromal, scleral, and uveal diseases.

A third research need in this area is the development of effective antiviral and anti-inflammatory therapies. Investigations should examine the role of topical and systemic antiviral agents and utilize information generated by research on herpes simplex infection. Problems of tear dysfunction, neuronal destruction, and epithelial regeneration should be explored.

Adenovirus and Enterovirus

An important research need for improved treatment of adenoviral conjunctivitis is the practical application of fluorescent antibody and other techniques which will aid in the early diagnosis of this disease. Results of these investigations could also significantly reduce its transmission. If significant data, which can be applied to clinical use, is to be obtained in one or two years, collaboration between virologists and clinical investigators is required.

It is also important to develop an animal model of adenoviral keratoconjunctivitis. However, the current methodology for these efforts does not seem to offer major opportunity.

Development of effective antiviral therapy is another important research need. Investigations could be linked with studies of herpes simplex and herpes zoster viruses.

The development of an effective vaccine to prevent ocular adenoviral infection is also important. However, this presently carries a lower priority because of the low severity of this disease and the estimated high developmental costs of such a vaccine.

Chlamydia

The development and application of practical and reliable methods of laboratory diagnosis of chlamydial infection are important needs. Such new methods would permit further definition of the incidence and significance of nontrachomatous disease in this country and be directly applicable to the worldwide problem of trachoma.

Another important need in chlamydia research is to determine the role of local immunity in primary infection and reinfection. The guinea pig model offers an opportunity to examine disease mechanisms in a relatively slow infection and may provide a clue to the mechanisms underlying disease produced by other infectious agents.

Bacterial and Fungal Keratitis

In bacterial and fungal keratitis, an important research need is to define the role of the host response in the pathogenesis of these diseases. Investigations should examine the significance of the host's immune system, the basic inflammatory response, and the production of endogenous enzymes such as collagenase and protease. Methods should be devised to block or alter these pathways.

Another research need is to define the role of microbial products in the pathogenesis of keratitis. Also needed are new, effective, and safe antibacterial and antifungal agents. They should be studied as they are developed by the pharmaceutical industry to ascertain if they can be applied to eye disease. These investigations should parallel other advances in general medicine. New techniques of drug delivery should be employed. Standard methods should be devised to measure levels of antimicrobial agents within ocular structures and to relate these levels to therapeutic needs.

Idiopathic, Peripheral, Infiltrative, and Ulcerative Keratitis

Although corticosteroids control many forms of peripheral inflammation, these diseases may progress despite multiple therapeutic efforts. Research is needed to define the multiple pathways of peripheral, nonmicrobial corneal inflammation and to provide effective methods of therapy.

Allergic Diseases of the Conjunctiva and Cornea

The major research need in allergic diseases of the conjunctiva and cornea is to develop effective methods of preventing and managing these varied disorders. These investigations should consider the potential efficacy of prostaglandin antagonists, nonsteroidal anti-inflammatory agents, and antigamma E compounds. New nonsteroid anti-inflammatory drugs should be developed and basic studies of pathogenesis should be performed.

Blepharokeratoconjunctivitis

Research is needed in blepharokeratoconjunctivitis to define the role of bacteria, bacterial substances, and host factors in the pathogenesis of these entities and to examine new methods of therapy, such as nonsteroidal anti-inflammatory agents, antitoxins, and immunopotentiators. There should also be study of their relationships to basic skin diseases and the effects of tetracycline and other antibiotics in small doses as well as other nonsteroidal anti-inflammatory agents.

The foregoing studies require the combined efforts of virologists, microbiologists, cell biologists, immunologists, immunopathologists, pharmacologists, and clinicians.

2

Dry Eyes and Tear Abnormalities, Epithelial Disorders, and Drug Delivery

THE MAINTENANCE OF a normal, healthy tear film/epithelium is an important deterrent to corneal disease. Prevention of the complications of tear film/epithelium abnormalities would greatly reduce surgical and hospitalization costs for these chronic, debilitating, and sometimes blinding diseases and disorders. Because of this, the entire subprogram is considered to be of the highest research priority.

Dry Eyes and Tear Abnormalities

The tear film is that surface of the eye most directly in contact with the environment. It is critically important for protecting the eye from external influences and for maintaining the health of the underlying cornea and conjunctiva. Numerous diseases adversely affect the tear film, causing conditions that, in turn, affect the cornea. The results range from low grade chronic eye irritation to severe discomfort and blindness. An understanding of the basic mechanisms of tear film formation, maintenance, and breakdown is essential to controlling and curing these diseases.

Disturbances of the tear film probably account for irritative eye symptoms in millions of Americans, although exact figures are not available. Such conditions are the result of environmental factors, such as fumes, smoke, and smog; infections and inflammations; age; lid defects; poor nutrition; systemic diseases; and drugs. The personal, social, and economic costs, in terms of chronic pain, irritation, and decreased vision with resultant loss of work, are considerable. Although blindness is not a common result of dry eye conditions, their widespread occurrence warrants considerable research on the tear film and on the relationship between lacrimal function and immunological disease.

The following is the clinical classification of tear film abnormalities:

- *Aqueous tear deficiencies* where the primary defect is in decreased secretion and/or excretion of lacrimal and accessory lacrimal glands
- *Tear film instability* which is characterized by abnormally rapid tear film breakup, possibly due to qualitative changes in tear film components such as mucus or to abnormalities of the epithelial surface

- *Surfacing problems* which include defects in lid form and movement and lid surface incongruity
- *Effects of agents* including effects of systemic medications, local drugs, contact lenses, smog, smoke, and fumes
- *Tear film drainage problems*

The following are important disease states where tear film abnormalities are the cause or an aggravating factor: keratoconjunctivitis sicca related to collagen diseases (as in Sjögren's syndrome), Riley-Day syndrome, congenital alacrimia, ocular pemphigoid, Stevens-Johnson syndrome, end-stage inflammation, chronic blepharitis, lid abnormalities, Vth and/or VIIth nerve paralysis, hypovitaminosis A, localized dry spots (dellen), contact lens-induced changes, drug-induced changes (systemic and local drugs), and epiphora. In addition, many elderly people without obvious disease commonly suffer from dry eyes, a condition which is frequently both uncomfortable and disabling.

Epithelial Disorders and Surface Injuries

Virtually all mechanical and chemical injuries to the eye, most ocular infections, and most damage to the eye from drying involve destruction of part of the corneal surface. Maintenance of an intact, healthy corneal surface is one of the most important requisites for normal vision. Diseases which disturb the integrity of this surface often cause decreased vision and result in severe pain and discomfort. Such diseases often result in irreversible scarring of the corneal epithelial surface, the most important refractive surface of the eye. Alternatively, such disorders may cause breakdown of the epithelial barrier to infectious diseases and can result in a permanently unstable epithelium which suffers chronic recurrent breakdowns. These conditions cause pain and suffering, often severe enough to render the victim unable to work, and often require frequent and expensive visits for highly skilled eye care. Because such injuries and epithelial damage are so common, even modest improvements in understanding epithelial healing and in developing means of stimulating it would have considerable social and economic impact.

The effects of recently developed contact lens materials on the epithelial surface also need to be studied. It is important to be certain that these appliances do not adversely affect the epithelial integrity and are compatible with the eye. Careful appraisal of the impact of environmental stress and pollution on the health of the surface of the eye is required, as well as evaluation of the effects of introducing increased numbers of drugs which can be applied directly or indirectly to the cornea.

Knowledge derived from basic and clinical investigations of the normal and pathological behavior of the corneal epithelium may be applied to other areas of biomedical science, such as dermatology, general nutrition, and metabolic diseases.

Drug Delivery

This is one of the most important areas in ocular care because drug delivery is an essential component of therapy. All new agents must be evaluated with this in mind. New delivery systems should be developed as a means of reducing the need

for frequent instillation or application of drugs, minimizing undesirable drug interactions and side effects, reducing costs, and increasing efficiency. In addition, the way drugs affect an individual's eye can provide clues to his or her genetic make-up.

In general, there are three major methods by which drugs gain entrance to the eye: by some sort of vehicle or delivery system to the surface of the eye, by periocular injection around the globe, and through systemic administration. Of course, drugs are administered to the eye for treatment of a wide variety of disorders not limited to the cornea and adnexa. In general, if any disease within the eye is to be treated, the safest and most desirable way of providing that treatment would be to apply the appropriate agent topically.

At the present time, the following are the most common methods of delivering drugs to the conjunctival cul-de-sac, the tear film, the corneal surface, and the intraocular chambers: drops (delivered directly from their container or indirectly by dropper or pipette), ointments, powders, iontophoresis, injections (including subconjunctival, subtenons, intracameral, and retrobulbar), dispensers which fit under the lid [lamellae and Ocuserts (see Figure 3)], packs (either cotton or gel foam), corneal baths, sprays (either ejaculator or misturizers), pumps, hydrophilic contact lenses, systemic applications, and irrigations.

Figure 3. Slow-release artificial tear being inserted into lower conjunctival cul-de-sac for treatment of chronically dry eyes.

Many of these methods vary in efficiency and efficacy depending on factors such as the characteristics of the vehicle (including its pH and tonicity, concentration, inclusion of surface-active additives, and persistence in the cul-de-sac and on the cornea), the chemical and physical properties of lamellae or Ocusert materials, and the drug's solubility.

The tear film/epithelium integrity plays such a basic role in protecting the eye from a variety of exogenous factors including smog, contact lenses, and ocular manifestations of systemic disorders that drug delivery systems which affect this interface have widespread economic importance. Such factors affect many people on a day-to-day basis; others, who have severe debilitating and blinding disorders, are affected chronically. In treating these conditions, more effort

should be devoted to developing better means of delivering existing drugs, rather than to developing new and more potent agents.

Accomplishments

Dry Eyes and Tear Abnormalities

In the past decade, considerable advances have been made in understanding the structure and formation of the precorneal tear film. It is generally accepted that the tear film consists of a thin (1000-2000 Å) film of meibomian lipid at the air/tear interface, which covers a four to seven micron-thick aqueous layer that contains salts, proteins, and mucin.[21] The epithelial surface is believed to be hydrophobic, similar to that of polyethylene; the adsorption of mucin renders it hydrophilic. The meibomian lipid film decreases the evaporation rate of water from the tear film.[22] Immediately after a blink the tear film has maximal thickness; subsequently, the thickness drastically decreases.

There is evidence that biochemical changes in aqueous tear composition occur as a result of disease and environmental influences. In particular, lysozyme[23] and tear albumin levels are known to fluctuate with disease. The importance of surface chemical factors in determining tear film stability has been substantially elucidated.[24] These factors also appear to dominate tear film formation and structure. Preliminary studies of the composition and surface chemical properties of meibomian secretion have been made.[25] It is likely that interaction between this superficial lipid layer and the tear film components is important for tear film formation and stability.

Tear flow dynamics and drainage have been intensively studied with the aid of fluorescein and radioactive technetium in normal individuals and in those with tear film disorders.[26] A number of tear substitutes have been developed, particularly by the pharmaceutical industry. These artificial tear solutions have irrigating and lubricating functions, and in many cases, mild vasoconstrictors have been added to them.

Epithelial Disorders and Surface Injuries

Scientists have found that many chronic epithelial defects and ulcers develop because the epithelium does not adhere properly to the basement membrane.[27] This has permitted the start of a rational approach to therapy. Morphological studies and scanning electron microscopy have delineated the appearance of the epithelium and some of the relationships between it and other corneal structures. However, much remains to be learned about the adhesion of the epithelium, its ability to heal and the control of such healing, the production of digestive enzymes which damage the cornea, and other factors.

Drug Delivery

Research on drug delivery and pharmacokinetics has been very fragmented. There has been a tendency for each drug or system to be tested as it becomes available using a research protocol of an individual investigator's own choosing. The results of such tests cannot, unfortunately, be compared with any previous studies. The most integrated scientific insights into the dynamics of drug movements in the eye have come from physiologists interested in the barrier properties of ocular tissues[28] and from pharmaceutical chemists interested in the

physicochemical properties of the drugs themselves, rather than from clinicians concerned with their therapeutic action.

From studies of a limited number of treatment modalities and chemical forms, a broad picture of the time course of a drug's concentration in various ocular media and how this varies with the drug's composition can be drawn. However, most of this type of information has been derived from the rabbit eye, which is known to differ significantly from the human eye in many ways, particularly in the frequency of blink rate—a major factor in determining the penetration into the eye of topically applied drugs.

Recently, several new dosage forms have been introduced, partly as a result of industrial enterprise and partly from academic investigation. These include the Ocusert,[29] various mechanical injectors, soft contact lenses,[30] and a number of viscous vehicles. The therapeutic adequacy of these forms has been unequally evaluated.

Research Objectives

- Determine the pathogenesis of dry eyes, tear abnormalities, and corneal epithelial disorders
- Improve the treatment of common eye irritations and chronically dry or inflamed eyes, thereby preventing their serious consequences
- Develop new methods of preventing and treating acute and chronic epithelial defects
- Evaluate the efficacy and applicability of available means of drug delivery and develop new and improved drug delivery techniques

Research Needs and Approaches

Dry Eyes and Tear Abnormalities

Because many hours of productivity are lost due to ineffective treatment of common eye irritations, especially dry eyes in the aged and those irritations suffered by contact lens wearers, much greater attention should be placed on preventing the more serious consequences of these conditions, rather than on treating them once they occur. It is imperative, therefore, that studies of new and old drugs be continued or initiated in order to provide pharmacogenetic and pharmacokinetic information that can facilitate therapy and reduce side effects. Specifically, the role of the constituents (vehicles, preservatives, drug concentrations) of various medications, their interactions with both the normal and abnormal tear film and epithelium, and the variable responses of patients to them have not been investigated in sufficient depth.

At present, it is estimated that the equivalent of only three Ph.D.'s are working full-time in tear research. In addition, about six clinicians are devoting a portion of their time to clinical research on dry eyes. It seems reasonable to expand this activity over the next few years. Although the need for surface chemists is probably satisfied for the moment, the field requires the efforts of additional biochemists with expertise in lipid and glycoprotein analysis, enzymology, and morphology. In addition, more postresidency clinical fellows should be trained in the various aspects of clinical research on dry eyes.

Epithelial Disorders and Surface Injuries

Prevention and treatment of longstanding epithelial defects are important priorities. These problems are of great importance because the stroma frequently ulcerates and sometimes perforates within the defect. In terms of visual impairment, disability, and cost, this disease category deserves top priority. The problem should probably be approached by attempting to understand how the epithelium adheres to its underlying tissue and by attempting to find epithelial growth stimulators. Improved soft contact lenses may also be helpful.

The intact but inflamed epithelium causes considerable discomfort and reduced vision. It is very important to find ways to ameliorate the chronically inflamed epithelium and to prevent its destructive effect on the stroma in terms of opacity and vascularization. Eyes that have had chemical burns or serious infections or that suffer from dryness are in this category. Such conditions are frequently bilateral and often afflict young people—two reasons their cost in human misery is so high.

The capability exists for investigating many research problems, answers to which should be directly applicable to ameliorating some of the following conditions: irritated epithelium (from infection, chemicals, drugs, ultraviolet light, environmental pollutants, and contact lenses), epithelial defects (including abrasion, recurrent erosions, and persistent epithelial defects), stromal-epithelial interactions in inflammation, epithelial dystrophies, pterygium and tumors, and epithelial edema caused by contact lenses.

Presently, only three Ph.D.'s in the United States are known to devote full time to solving epithelial problems. In addition, there are about a dozen clinical and basic investigators working part-time in this field. In view of the magnitude of epithelial problems in terms of discomfort and blindness, the manpower requirements for research in this area should double over the next five years. Cell biologists and experimental pathologists should be recruited and trained for this work. Training grants, supporting laboratory research scientists as well as clinicians, are vital in this effort.

Drug Delivery

Thorough evaluation of the efficacy and applicability of various available methods of drug delivery is greatly needed. Measurements should be made of a drug's bioavailability-penetration rate, duration, and metabolic breakdown. Biochemical tests should include direct analyses and study of factors involved in biological variability of drug response in laboratory animals and humans.

Evaluation of these methods should take into account the status of the eye, whether normal or inflamed, and how this influences drug penetration. It should also take into account whether the epithelium is intact or broken, the status of the tears and tear film, the reaction of tears to the drug under study, the role of the corneal-conjunctival adnexa as a reservoir (the general problem of drug kinetics), and the influence of protein binding of tear contents. ocular tissue, and fluids on drug action.

Further evaluation should include consideration of the therapeutic efficacy of the drug on controlled lesions in laboratory animals where possible; therapeutic efficacy in the human eye; the influence of various methods of administering drugs on tissue tolerance, function, and anatomic integrity; and the interaction of a drug with other simultaneously administered agents, whether systemic or topical. The latter study should include the role of the vehicle, e.g. preservatives, stabilizers, and the tears themselves, in drug interaction.

The problem of ocular drug administration and drug delivery is in a sense subspecialized. Nevertheless, it seems that every effort should be made to encourage pharmacologists to commit themselves further to the study of ophthalmic pharmacology. Because there are few trained ocular pharmacologists, high priority should be given to training such individuals in an atmosphere in which clinical and basic pharmacology are both under study.

Priorities and Recommendations

Dry Eyes and Tear Abnormalities

- Determine the composition and biophysical characterization of individual glandular secretions in corneal health and disease
- Describe immune mechanisms in lacrimal gland dysfunction
- Study tear flow and drainage problems and the control of normal tear secretion
- Study physicochemical stability of the tear film and how this is affected by environmental and emotional factors and drugs
- Study blink mechanisms and blink stimulation
- Analyze specific proteins in the tears in eye diseases
- Improve the clinical diagnosis of tear-deficient states
- Develop a means to diagnose systemic diseases from tear analysis

Epithelial Disorders and Surface Injuries

- Study the adhesion between the epithelium and underlying tissue
- Search for epithelial growth stimulators
- Find means of ameliorating chronically inflamed epithelium
- Prevent destructive effects of epithelial opacity and vascularization on the stroma

Drug Delivery

- Develop, evaluate, and compare new and existing means of drug delivery
- Study the pharmacokinetics of drugs used in and on the eye
- Determine genetic influence on drug reactions

Resource Requirements

Fiscal year 1977 funding for this subprogram will be approximately $591,000 to support eight research grants and one specialized clinical research center grant. The Panel recommends an additional 17 research grants for this subprogram, bringing the total funding in fiscal year 1978 to $1,864,000. See the tables at the end of this report for further details.

3

Refractive Problems and Contact Lenses

THE PANEL HAS selected Continuous-Wear Contact Lenses, New Contact Lens Materials, and Orthokeratology as the research areas of highest priority within this subprogram. (For additional discussion of research related to the development and progression of myopia, see Chapter 3 of the report of the *Retinal and Choroidal Diseases* Panel.)

Nearly 94 million people in the United States wear eyeglasses or contact lenses to improve their vision. Most of these people have refractive errors: nearsightedness (myopia), farsightedness (hyperopia), astigmatism, and other conditions. Usually, refractive errors are not serious and can be easily corrected with prescription lenses.

The annual cost of visits to ophthalmologists and other physicians for refractive errors is estimated to be $150 million annually. The cost of optometrists' services and materials per year is almost $1.2 billion, of which the greatest portion is for the correction of refractive errors.

When light enters the normal eye, it is refracted or bent by the cornea and by the lens. These tissues bend or refract the light so that it is brought to a single, sharp focus on the retina, the light-sensitive tissue at the back of the eye. Here, light impulses are converted to nerve impulses and are transmitted to the brain where they are interpreted and vision takes place.

In the normal eye, clear vision depends upon the existence of a precise relationship between two eye measurements: the refractive power of the cornea and lens and the length of the eye. Any variation in this relationship results in a blurred image or refractive error. The cause of this variation is usually unknown, but both environmental and genetic factors may play a role in the development of refractive errors.

Continuous-Wear Contact Lenses

Those wearing contact lenses can be divided into two categories. The largest group, perhaps 7 million people in the United States, wears contact lenses optionally as an alternative to eyeglasses. The second group, which numbers about 1 million people, requires contact lenses because of pathological conditions of the cornea or to provide better vision following surgical removal of cataract. It is this latter group for which extended- or continuous-wear contact lenses would be most beneficial since a large portion of these people have great difficulty in manipulating contact lenses or are simply unable to handle them at all. This is

especially true of elderly patients who have had cataract surgery. In addition, many pathological conditions of the cornea require that the lenses be worn continuously during sleep as part of the therapeutic process. The potential use of extended-wear or continuous-wear soft lenses as a mode of drug delivery to the eye has just begun to be explored.

New Contact Lens Materials

Many new polymers have been developed and are undergoing experimentation for possible use as contact lens materials. There is great potential for materials with properties superior to those in use today, particularly with regard to gas permeability, wetability, surface quality, optical quality, durability, and stability.

The development of better materials for continuous-wear lenses would benefit a large number of aphakic and corneal disease patients, as described above, as well as those ametropic patients in our society who desire this method of visual correction. The development of rigid lenses with qualities superior to polymethylmethacrylate (PMMA) is needed for keratoconus patients, those with a high degree of astigmatism, and those afflicted with corneal distortion and other conditions not adequately corrected by lenses made of flexible materials.

Orthokeratology

Orthokeratology consists of fitting a series of specially designed, slightly flattened contact lenses which gradually remold the cornea. There have been numerous studies and publications concerning the effects of contact lenses on corneal integrity, curvature, topography, and changes in the refractive error of the eye. The causes and mechanisms for these alterations are either not known or not agreed upon by vision scientists. Advocates of orthokeratology claim to make constructive use of these changes without sacrificing corneal or ocular integrity or vision.[31] The exact degree of benefit and the risks involved remain to be defined scientifically. Should such a procedure be found to be effective and generally safe, the impact on that portion of society afflicted with refractive errors could be significant. Those with myopia would, of course, be the major beneficiaries. Further refinement of orthokeratology would also permit a better understanding of the corneal response to contact lenses in general.

Accomplishments

Continuous-Wear Contact Lenses

For most people with refractive errors, corrective eyeglasses or contact lenses provide simple and highly satisfactory restoration of clear, sharp vision. In recent years, the introduction of hydrophilic, flexible, soft contact lenses has broadened opportunities for treatment of refractive errors. Figure 4 shows the eye of a patient who, after cataract extraction, has worn soft contact lenses almost continuously for three years, with excellent visual correction and no complications. These contact lenses have made possible the correction of irregular corneal surfaces which previously had been extremely difficult or impossible to treat. They have also made it possible to provide comfort, protection, and useful vision

shortly after corneal transplant surgery, in the presence of bullous keratopathy, or in certain very debilitative dry eye syndromes.[32] Soft lenses also enormously simplify the refractive correction of the newborn and young, and they provide a means of correction for many who are unable to wear hard contact lenses.

Figure 4. Arrow indicates the edge of a continuous-wear contact lens.

Yet, today's soft lenses only represent the beginning of a new era in contact lens design. Presently available soft lenses are not as effective optically as hard contact lenses. They require more care and maintenance and are not as durable as the hard lens. However, these new contact lenses raise the possibility of providing a full-time correction that need not be removed at night. Such a method would be ideal, especially for the young, the elderly, the infirm, and those with aphakia or generally poor vision. In fact, the possibility exists that continuous-wear contact lenses may eventually replace eyeglasses as the best means of correcting optical abnormalities. Enough experiments have been conducted to show that this goal is feasible, and several types of continuous-wear lenses are now being studied commercially. This development may also eliminate the use of intraocular lenses for the correction of aphakia.

New Contact Lens Materials

The development of new contact lens materials has dramatically changed this field. Soft contact lenses can permit instant, comfortable wear for prolonged periods of time. Newer materials which permit greater oxygen permeability are under study for use in contact lenses which may be worn continuously without damaging the cornea. With the use of both soft and hard lenses, it is possible to provide adequate visual function for many patients who are visually handicapped or even legally blind.

At present, a few practitioners are experimenting with having their patients wear soft hydrogel contact lenses continuously. They have experienced mixed results. In some patients, the response is very good; they seem to have no difficulty in wearing the lenses. In other patients, massive edema is produced and

the lenses become intolerable. The reason why such variability in response occurs is unknown and should be investigated. Continuous-wear soft contact lenses can be looked upon as a realistic goal that can be achieved in a relatively short time.

Polymethylmethacrylate (PMMA) contact lenses have been used successfully by a large number of patients for years. Many others have not been able to wear them or have stopped wearing them for a variety of reasons including discomfort, optical problems, and improper handling. Nonetheless, this type of contact lens is still the one of choice for many refractive conditions such as high astigmatism, corneal distortion, and other cases where hydrogel lenses are not suitable.

Orthokeratology

Orthokeratology has been developed as a mechanism by which hard contact lenses can be placed on a cornea to change its shape and reduce the degree of myopia. Some practitioners, primarily optometrists, believe they have demonstrated that orthokeratology can reduce myopia and in some cases eliminate the need for glasses or conventional contact lenses. More precise studies are needed concerning the risks involved, changes in corneal shape produced, maximal degree of correction obtained, and the duration of such correction. Such prospective studies should help settle the controversy concerning this procedure and provide objective data for rational evaluation of its safety and usefulness.

Research Objectives

- Develop a contact lens for refractive correction that can be worn continuously with comfort and safety
- Evaluate the usefulness of such a lens as a means of drug delivery
- Develop and improve new contact lens materials and determine their effects upon corneal physiology and metabolism
- Resolve current problems with hydrogel lenses
- Improve instrumentation to evaluate the design, fit, and effects of contact lenses
- Determine the extent of correction obtainable by orthokeratology and its duration and risks

Research Needs and Approaches

Continuous-Wear Contact Lenses

Hydrogel lenses have been available to the general public since 1971. The current state of the art indicates a need for further refinements in both the cosmetic and therapeutic uses of these lenses and for their further development as vehicles for drug delivery. Yet, the evolution of soft contact lenses is hampered by the lack of instrumentation for measuring physical parameters, the composition of lens materials, the state of manufacturing technology, and by the absence of a detailed study of the effects of such lenses on corneal metabolism and physiology.

The effects of new soft lenses, which are intended for continuous-wear, upon corneal physiology need to be assessed. The causes of superficial vascularization,

which occurs in certain patients who have worn such lenses for extended periods of time, have to be defined. Criteria for the safety of each new type of lens material must be established. Studies should weigh any possible risks against the potential advantages of these lenses: extended wear, comfort, and other factors.

At present, because continuous-wear contact lenses are not available for other than investigational use, the surgical treatment of cataract often involves the insertion of a plastic lens within the eye. There is no question that the insertion of such a lens, after the natural cataractous lens has been removed, is a delicate and difficult additional surgical step which contributes incremental risks and complications. (See report of the *Cataract* Panel.) A continuous-wear contact lens could serve as an alternative to the intraocular lens, contributing not only to greater safety but to greater flexibility in changing the refractive correction, should that need arise.

Many long-term effects of hard contact lenses such as corneal shape changes and physiological effects are not fully understood but are of great clinical importance. New designs, such as aspheric surfaces and ultrathin lenses, are now being introduced. The scientific community needs to determine the clinical value and importance of different designs, the types of patients for which they can be optimally used, and their short- and long-term physiological effects. Such evaluative information is generally not provided by manufacturers.

Perhaps the most important research need in this area is to develop and improve contact lens materials to resolve the problems associated with current hydrogels. An additional research need is to determine further the effects of hydrogel contact lenses on visual and optical performance. Adequate instrumentation is needed to measure lens parameters accurately.

Although most of the material development will come from private industry, under Food and Drug Administration guidance there should also be some independent tests of the safety, efficacy, and uses of these materials. Resolution of present problems may lead to lenses that can be worn both continuously and safely.

New Contact Lens Materials

As noted above, responsibility for the development of new materials and for setting standards for their safety is mostly borne at present by the manufacturer. However, determining the properties required for maintaining normal physiology and establishing standards for clarity, surface quality, and durability must be the responsibility of the scientific community. In addition, scientists must determine the guidelines for quality and the limits within which there can be acceptable trade-offs. For example, independent investigators must determine how much of a decrease in clarity or durability can be accepted in exchange for a significant increase in oxygen transmission or in permeability to small molecules. Many other possible trade-offs will have to be considered.

Both short-term and long-term benefits can be realized: guidelines written by scientists which define the quality of lenses and their desired properties can act as an impetus to more rapid development of better materials, thereby affording present and future contact lens wearers the earliest possible benefit without undue suffering or risks. Such guidelines can also help define long-term goals for materials development.

No awards have been made by NIH for the development of new contact lens materials. The present need is great, especially in view of the widespread use of new materials in treating many ocular disorders. This is the opportune time to determine guidelines and evaluate new materials. High priority should therefore be given to studies in this area.

A team of scientists who are independent of lens manufacturers should evaluate the qualities of new lens materials as they become available. The practitioner may then directly compare properties tested under exacting scientific conditions. With such information, the practitioner can determine which lens material is best suited for a particular patient's needs. These careful clinical studies should include documentation of corneal thickness, vascularization, and potential complications. In addition, instrumentation to evaluate lens geometry, edging, bevels, and design should be improved.

Orthokeratology

Because of their purely clinical approach, previous studies in orthokeratology have been limited by inadequate controls. Although there have been a few quantifiable studies, new, impartial, carefully controlled clinical trials are required to determine how well orthokeratology can correct refractive errors, the duration of correction, and the complications and risks involved. The National Eye Institute is now funding one such study, but it seems that other independent investigators, which may be multi-institutional and involve participants from a variety of scientific disciplines, would be worthwhile. Each study should have a randomized control group to determine the natural course of myopia and the natural incidence of problems which might also occur in the orthokeratology group. Both ophthalmologists and optometrists should contribute to such studies.

Priorities and Recommendations

Continuous-Wear Contact Lenses and New Contact Lens Materials

- Determine effects of new contact lens materials upon corneal physiology and metabolism, and discover the cause of superficial vascularization from extended wear.
- Establish criteria for the safety, efficacy, and uses of new lens materials. Evaluate different lens designs on different types of patients, and resolve problems observed with current hydrogel lenses.
- Study corneal metabolism, hydration, and physiology in patients wearing contact lenses continuously, and improve instrumentation used to evaluate lens geometry, edging, bevels, and design.

Orthokeratology

- Determine the extent and duration of correction obtained by orthokeratology and the risks involved in this procedure.

Resource Requirements

In fiscal year 1977, the NEI will fund no projects on *Refractive Problems and Contact Lenses*. The Panel recommends the initiation of eight research grants at a total

funding of $599,000 for FY 1978. The tables at the end of this report include a list of recommended projects.

Other Important Research Areas

The Panel believes that research in the following areas—Corneal Physiology, Keratoconus, Astigmatism, and Corneal Distortions—though important, is of a relatively lower priority within this subprogram.

Corneal Physiology

Contact lenses, hard and soft, now represent a considerable portion of refractive corrective prescriptions. They are frequently the only acceptable corrective form available to minimize the optical problems of monocular aphakia, to "resurface" optically the irregular cornea, to provide mechanical protection for the cornea with bullous keratopathy, and to treat many other pathological conditions. However, neither the short- nor long-term effect of hard and soft contact lenses on the physiology of healthy or diseased corneas has been fully defined.

Keratoconus

Keratoconus is a noninflammatory, progressive, chronic deformity of the central portion of the cornea. It is characterized by corneal protrusion and thinning, with structural changes becoming apparent in the later stages. The conus varies in degree from a mild form, which can be corrected with glasses, to a more advanced form, which is commonly corrected with contact lenses. A patient whose condition progresses beyond the stage where contact lenses may be worn usually receives a corneal transplant.

Astigmatism and Corneal Distortions

Eyeglass correction of astigmatism, particularly after cataract surgery, is rarely an important problem. However, adequate visual restoration in the aphakic, astigmatic patient with any type of contact lens, but particularly with soft contact lenses, represents a serious problem. Corneal astigmatism resulting from penetrating keratoplasty is the most frequent disabling complication of this procedure and the most difficult to manage successfully. It almost always significantly affects the binocularity and productivity of the affected patient.

There are major problems in providing adequate optical correction to patients with complex corneal pathology. Included in this group are individuals with keratoconus and Terrien's disease, as well as patients who have had corneal transplants, ulcerations or infectious diseases, and other anomalies. These conditions result in grossly distorted corneal surfaces, high astigmatism, and either low or high corneal curvature.

Accomplishments

Corneal Physiology

A series of studies have been done both by optometric institutions and ophthalmology departments on the cornea's requirement for oxygen and the ability of contact lenses to pass oxygen to the cornea. These have resulted in clear

knowledge of the properties needed by soft contact lenses if they are to become useful for permanent-wear and have also contributed to understanding of corneal edema resulting from contact lens wear. In addition, studies of methods to measure corneal topography and the general corneal shape have made possible much of the research now being conducted by commercial companies on soft contact lens materials that will meet the needs of the cornea. Much of this landmark research was done after the development of the first soft contact lenses, which themselves enabled great progress to be made.

Keratoconus

Thermokeratoplasty is the first surgical procedure to be developed for the treatment of keratoconus since corneal transplantation.[33] However, the success rate of this technique varies widely from research center to center, some studies have not found it to be of lasting value, and all have found it to be unpredictable. Its potential, however, remains sufficiently exciting and indicates that further research seems appropriate.

Astigmatism and Corneal Distortions

Attempts to control corneal astigmatism by surgical means are not new; the earliest report dates back at least 100 years. The following procedures have been advocated in the past: superficial cauterization, Sato incision, wedge resection, thermokeratoplasty, and control of the cataract extraction wound at surgery. Thermokeratoplasty, mentioned above, is used mainly to treat keratoconus by shrinking the corneal stromal collagen. Its use has been limited because it can only steepen a flat meridian and because available data concerning its advantages and disadvantages are insufficient.

The type and amount of astigmatism following cataract surgery can be controlled by placement of the incision, regulated closure of the cataract wound, the type of suture and suture technique, and the time of suture removal. Similarly, wedges of cornea have been excised from the periphery of a flat meridian in order to steepen that meridian, but the results were not obtained under exacting conditions. More precise control techniques are needed.

Research Objectives

- Determine the effects of contact lenses on the physiology of normal and pathological corneal tissue
- Reevaluate and standardize thermokeratoplasty as a treatment for keratoconus
- Improve treatment of astigmatism and corneal distortions
- Improve mensuration of corneal refractive problems

Research Needs and Approaches

Corneal Physiology

Industry today is developing new contact lenses without an adequate understanding of the corneal response. For the protection of the public, it is imperative that the scientific community independently evaluate the effects of these lenses. These evaluations cannot, however, be made without a better knowledge of basic corneal physiology.

Longitudinal follow-up studies are needed to determine the effects of contact lens wear on the oxygen requirements, enzyme activity, ATP concentration, and glycogen content of the normal epithelium and endothelium. The effects of contact lenses on stromal collagen and ground substance—for example, in terms of curvature stability and hydration state—should also be studied.

The same questions should be answered for the diseased cornea, but such secondary complications as chronic edema and neovascularization and the effects of contact lenses on epithelial and stromal healing processes should also be evaluated.

An important clinical need is to develop new types of contact lenses which effectively provide critically needed optical and protective benefits while imposing minimal physiological stress on the cornea (for example, by providing adequate gas exchange, negligible reflex tearing, and long-term compatibility with the tear environment). These studies may be performed independently or in conjunction with studies of continuous-wear lenses. They would require research groups composed of optometrists, ophthalmologists, physiologists, and polymer and physical chemists.

Another important research need is to define corneal metabolism and physiology in patients wearing contact lenses continuously. Energy metabolism, oxygenation, and hydration of the cornea require special consideration. Careful clinical study is also essential to document changes which occur over a period of time. Physiological studies of corneal metabolism and hydration should be performed using both laboratory animals and human volunteers.

Keratoconus

Standardization of thermokeratoplasty is of the utmost importance if this technique is to gain wide acceptance as a possible treatment for keratoconus. The effect of thermokeratoplasty on the human corneal endothelium must be reevaluated by pachometry, specular microscopy, and other techniques. A controlled study is needed in which conus patients would be randomized into two or more groups. All patients with conditions that are not correctable by lenses would be treated with either thermokeratoplasty or keratoplasty. These patients should be selected at random for either treatment, and their vision should be measured by another investigator. Such a trial could provide an objective comparison of the two treatment methods.

Astigmatism and Corneal Distortions

There should be improved identification and assessment of factors which reduce the quality of the optical image. These include folds in Descemet's membrane, clouding of the cornea or other optical media, aberrational defects in ocular or corrective lenses, off-axis pupillary location, and the presence of multiple pupillar apertures whether postsurgical, traumatic, or degenerative. Suitable treatment regimens for such problems should also be explored.

Studying the cornea at the time of eye surgery with a device for measuring astigmatism and topography would help to determine the proper suture and wound closure technique to use in correcting preoperative astigmatism. Postoperative corneal topography, central keratometry, and corneal thickness, in addition to the refractive error, can serve as guides to the surgeon who must decide which meridian needs to be steepened. Such measures to prevent postoperative high astigmatism will make it possible to provide better visual correction with eyeglasses and contact lenses for people undergoing cataract surgery or corneal transplantation.

Large numbers of patients would be required for a study of such procedures in order to assure accurate statistical analysis, and a follow-up of at least six months would be required. Such a study could be accomplished at two or three centers over a period of one or two years.

Mensuration and Epidemiological Aspects of Corneal Refractive Problems

By comparison with the preceding topics, mensuration of corneal refractive problems is a lower priority area for study, but nevertheless one which could have significant impact on understanding of the visual mechanism.

The group most likely to benefit includes infants with high refractive error or those who have a high genetic probability of developing refractive errors and can be identified before their sensorimotor processes are irreversibly impaired. Individuals afflicted in their infancy by deprivation amblyopia, strabismus, or nystagmus often suffer lifelong restrictions and frequently become dependent on public support for their entire lifetimes.

A fundamental key to the prevention of long-term functional defects of the visual system, for example, amblyopia, loss of binocularity, and nystagmus, is to have an accurate quantitative description of how contributing ocular structures change with age. Optically, the most critical of these tissues is the cornea because of its susceptibility (largely genetic but also due to disease) to abnormal spherical and astigmatic curvatures.

4

Corneal Edema, Dystrophies, and Inherited Disorders

THE PANEL DETERMINED Endothelial Morphology and Function In Vivo to be of highest priority within this subprogram.

The fragile endothelial layer which lines the inside of the cornea is critically important in maintaining proper hydration of corneal tissue. Endothelial failure leads to corneal edema which results in decreased corneal transparency, poor vision, and often severe pain. Many older people suffer from a spontaneous deterioration of the corneal endothelium, a condition known as Fuchs' dystrophy. Unfortunately, this often blinding disease usually affects both eyes.

Endothelial Morphology and Function In Vivo

Injury to the endothelium may occur inadvertently during intraocular surgery, such as for cataract, or as a result of chemical and mechanical injury. Endothelial cell destruction from ocular disease is also not uncommon. Long-term treatment with drugs is also suspected as a cause of injury to the endothelium, particularly where its function is already compromised by age. Abnormal systemic conditions can probably influence the health of the corneal endothelium, although virtually nothing is known about this. Fuchs' dystrophy, the most common endothelial degeneration with aging, for example, occurs about three times more commonly in women than in men and may be influenced by the effects of hormonal changes associated with aging.

Because endothelial dysfunction is usually permanent, corneal transplantation may provide the only hope for restoration of vision. But, success of the corneal graft also depends on the adequate function of its endothelial layer.

The cornea is the only human tissue, apart from the lens of the eye and cartilage, that has no blood vessels. This provides the scientist with unusual opportunities to study, without immediate interference from the blood supply, normal function and pathological reactions, either in vivo or in simple in vitro perfusion systems. Furthermore, the transparency of the cornea allows cell morphology to be observed under functional conditions and even in vivo. This has attracted a number of basic scientists in physiology, as well as in immunology and pathology, to study the cornea as a model for cellular activities that also take place in other parts of the body.

In particular, it should be noted that Fuchs' and other dystrophies of the cornea are probably examples of how aging affects other organs of the body. Understanding the normal function of the endothelium and connective tissue of the cornea and how they are degraded by these dystrophies may lead to insights into human aging in general.

Accomplishments

Research with animals, in particular, rabbits, has provided a great deal of valuable knowledge about the function of the endothelium, both as a fluid barrier and as a metabolic pump.[34,35] However, the human endothelium is unique in certain ways: for example, its inability to regenerate and its susceptibility to certain dystrophic changes limit the applicability of findings from studies of the corneal endothelium of animals to human eye disease. In vivo studies in humans are therefore necessary. The use of the specular microscope as a simple clinical examination technique has provided a means of doing this. Preliminary studies with this instrument have documented previously undetected endothelial cell loss from certain successful ocular surgical procedures, such as cataract extraction and intraocular lens insertion.[36] An estimate of endothelial function in vivo can be obtained from fluorescein permeability studies and by measurement of corneal thickness.

Research Objectives

- Understand the normal function of the endothelium and connective tissues of the cornea and how they are degraded by injury and disease
- Improve and standardize instrumentation for investigating endothelial morphology in vivo
- Determine the usefulness of endothelial cell assessment as a clinical prognostic indicator
- Explore the nature and pharmacological modifications of the endothelial pump

Research Needs and Approaches

Improvements in the design and instrumentation of clinical endothelial examination techniques should be encouraged. The limitations of specular microscopy and fluorophotometry and the significance of observed morphological and functional changes require definition. Additional knowledge of endothelial regenerative capacity, the endothelial effects of intraocular surgery, and the characteristics of endothelial diseases is needed. An attempt should be made to estimate more accurately the capacity of individual corneal endothelia to withstand different intraocular surgical procedures. Scientists need to understand the relationship between endothelial cell population density and the capacity of the cornea for healing.

Endothelial damage which occurs during cataract extraction or corneal transplantation may not become clinically evident as corneal edema with loss of vision for several years following surgery. With specular microscopy, such

endothelial damage can now be detected immediately following the operation, thereby permitting a more objective comparison of the effects of different surgical procedures. In addition, examination of the endothelium of patients prior to surgery may help identify those eyes that are less able to withstand the operation. Objective data, such as the endothelial population density, may be useful to the ocular surgeon in deciding if an operation will be tolerated at a particular time and which surgical technique should be used.

Observations of the endothelial effects of various drugs and of different methods of corneal preservation upon the endothelium of transplants have immediate applications. Similarly, the irrigating solutions now used in intraocular surgery have become increasingly important because of the large volumes which are needed for vitrectomy operations (see Chapter 9 of the report of the *Retinal and Choroidal Diseases* Panel). Such operations may produce corneal edema, and some data suggest the need for further study of irrigating solutions which minimize endothelial damage. Long-term studies of endothelial healing, the development of endothelial dystrophies, and the effects of chronic drug administration upon the endothelium have significant potential for payoff.

Long-term studies of the possible repopulation of the endothelium as an alternative to keratoplasty should be encouraged. If success is achieved in the rabbit, extension to primate models should be initiated and then, finally, trials in humans should be undertaken. The collection of sufficient human endothelial cells for culturing and clinical testing may require the cooperation of more than one research center.

Studies of endothelial function and morphology in vivo should receive high priority because adequate techniques are available for such investigations, and the expected results would be immediately applicable to reducing human visual loss. These studies will require clinical investigators to study the effects of various manipulations on the endothelium. In addition, at least two or three groups should work on each of the following: improvement of instrumentation, the correlation between endothelial morphology observed by specular microscopy and that observed by standard electron microscopy, and functional studies, such as fluorometric measurement of endothelial permeability.

Priorities and Recommendations

- Determine endothelial regeneration capacity, the effects of different surgical and transplantation procedures upon the endothelium, the characteristics of endothelial diseases, and the effects on the endothelium of various drugs and different methods of corneal preservation
- Utilize new information on the endothelial pump to explore further its function, and study the effect of drugs on corneal hydration
- Improve the design and instrumentation of clinical endothelial examination techniques
- Establish the limitations of specular microscopy and fluorophotometry in determining corneal morphological and functional changes
- Study the possible repopulation of the endothelium as an alternative to keratoplasty

- Develop routine procedures for gathering objective data such as endothelial population density in order to help the ocular surgeon decide if an operation will be tolerated and which surgical technique should be used

Resource Requirements

The Panel recommends eight new research grants in the area of Endothelial Morphology and Function In Vivo, bringing the total number of research grants in the subprogram to 39, with a total FY 1978 funding level of $2,616,000. See the tables at the end of this report for an itemized list of recommended new projects.

Another Important Research Area

Corneal Dystrophies and Inherited Disorders

The Panel determined that research on Corneal Dystrophies and Inherited Disorders, though important, has a lower priority within this subprogram.

Corneal dystrophies can be divided into those problems concerned with early development and those related to aging. Although they are not a major cause of blindness, they can cause considerable discomfort and inconvenience to those they afflict. Because of their high prevalence, they have substantial social and economic importance.

A significant number of corneal disorders are caused by untoward genetic or environmental influences. In rare cases, affected individuals are blind from birth with tragic consequences for themselves and their families. More frequently, hardship is caused by partial disablement and the need for continuing medical care. A relatively more prevalent disorder is keratoconus which affects people at an early age and causes bilateral, life-long disability. The progress of this disease generally goes unchecked unless expensive keratoplasty treatment is employed.

The ametropias, a very large group of visual disorders which are influenced by genetic or environmental factors, are also important. These range in severity from inconvenient, small refractive errors which are correctable with eyeglasses or contact lenses to malignant myopia which can ultimately result in blindness.

As mentioned above, in some people aging causes deterioration of the corneal endothelium, producing the problem known as Fuchs' dystrophy. This condition is, unfortunately, usually bilateral.

Another effect of aging is the premature or excessive deposition of various biochemical substances within the cornea. Such depositions can occasionally cause visual loss. Studying them may improve understanding of disorders of the body as a whole.

In addition, exogenous insults need to be considered. Climate, for example, appears in some obscure way to be able to cause severe, bilateral blinding deterioration of corneal tissues as in actinic or climatic keratopathy. Pterygium, a very prevalent condition, also appears to be related to climatic factors, as do benign and malignant squamous neoplasms of the conjunctiva and cornea.

Accomplishments

Very few studies of the cornea have employed either tissue culture or somatic cell genetics. However, many researchers are now beginning to utilize these new

techniques with corneal tissue in order to study genetic defects. At present, three investigators are carrying out NEI-funded corneal research involving tissue and organ culture studies.

Research into the basic physiology of the limiting cellular layers of the cornea is well-supported by the NEI. The roles of the two layers involved in the control of corneal hydration has been established,[34] and advances are being made in understanding the basic biochemical mechanisms underlying their function.[36-39] Progress has been slowed to some extent by the fragility of these layers, particularly the endothelium, and their limited survival time in vitro. Studies are underway to improve cell survival in organ culture[40] and also to establish confluent cell monolayers in tissue culture. These may show the functional behavior of the normal cell layer.

Research Objectives

- Determine the effects of genetic and environmental influences on normal corneal development and metabolism
- Determine the effects of aging and stress on the morphology and function of the cornea

Research Needs and Approaches

Corneal dystrophies, which generally represent more of an inconvenience than a cause of major visual impairment, must nevertheless be considered of major importance. Although many of the more serious conditions can be cured by keratoplasty, their prevalence is expected to increase as the Nation's population increasingly ages. Not only will investigations into corneal dystrophies improve understanding of these ocular diseases, but as was mentioned above, it is probable that such studies will contribute important information concerning aging in general.

Some of the important needs in this field of research are discussed below:

Study of the Synthesis of Collagen and Polysaccharides by Cells from All Layers of the Cornea in Tissue Culture and of How This Process is Modified in Genetic Disorders

Errors in synthesis and maturation of both proteoglycans and collagen have been found in other disorders such as systemic mucopolysaccharidoses, Ehlers-Danlos syndrome, and osteogenesis imperfecta. Many new techniques are now available for studying normal and abnormal corneas. These involve growing whole corneas (as organ cultures) or dispersed cell cultures in vitro and analyzing the products of normal and abnormal cells. These methods enable ophthalmic scientists to study large populations of cells from relatively few donors.

The study of genetics may in fact shed new light on the whole idea of dominant and recessive metabolic diseases. The fact that mucopolysaccharide storage diseases such as Scheie's syndrome, macular dystrophy, and such abnormalities of connective tissue as lattice dystrophy can be truly inherited metabolic degenerations, yet apparently be totally organ-specific, suggests that other organ-specific diseases which occur later in life may have a genetic basis.

Differentiated cell lines in culture may express genetically caused metabolic defects even when these cells appear to be unaffected by the disease. These investigations can be related to studies of other tissues, such as skin from

individuals with other inherited defects, and thereby may provide information concerning the general pathway of connective tissue synthesis and maturation.

Tissue culture studies enable researchers to manipulate readily the environment around cells and may thereby suggest methods for regulating abnormal production, or lack of production, of the cells' products, including collagen and proteoglycans.

The costs of tissue culture are relatively large, but the expected payoffs in a relatively short time should be considerable. This could be particularly important because little information has been obtained from in vivo studies. Tissue culture seems to be the only accurate way to study many of the heritable corneal dystrophies. In contrast to the long time span involved with classical genetic studies, somatic cell hybridization can give precise information in months rather than decades.

Very few studies have been performed using either corneal tissue culture or somatic cell genetics. Multicenter and multidiscipline studies would require the combined efforts of ophthalmologists, cell biologists, cytogeneticists, and immunologists.

Developmental Studies in the Mammalian Cornea

Many corneal defects originate in untoward genetic or environmental influences during prenatal development. In the past, animal models have supplied information about the roles in normal development of a variety of factors including tissue interactions, endocrine influence, and mechanical input.

Experimental studies of sensitive periods during corneal development are needed to identify those steps in corneal morphogenesis which are most sensitive to disruptive influences. Such periods usually correspond to the times during which the cornea is influenced by adjoining ocular tissues. Studies have demonstrated that thyroxin influences corneal development, but scientists need to study the roles played by other endocrine substances in the normal and abnormal development of the cornea.

The developmental sequence of roles played by the three types of corneal cells, including their changing capacities for synthesis and transport of macromolecules which make up the cornea, has been only partially elucidated by recent investigations. The production of basement membrane by the corneal epithelium and the developmental significance of their sequence needs to be further explored. It is important to determine whether in mammals a primary stroma is secreted by the embryonic corneal epithelium, as it is in some submammalian forms.

Many corneal defects involve aberrations in the growth or remodeling of the cornea. The cell population dynamics (cell division, migration, death, and differentiation) of the epithelial, endothelial, and keratocytic cell populations should be assessed. The mechanisms involved in remodeling during development of the extracellular matrices (Bowman's membrane, the stroma, and Descemet's membrane) must be defined if the types and limitations of controls on the cornea's normal growth and development are to be understood.

It is also important to identify the roles of the factors which control the development of eye shape. Knowledge of such factors would be an important step in elucidating the etiology of some forms of refractive error, providing a rational basis for assessing the risks of developing such errors, and developing means for minimizing or preventing anomalous, disabling shaping of the eyeball which results from environmental influences. The NEI currently supports two studies in this area; more are needed.

Study of Aging and Stress on the Function and Morphology of the Endothelium and Descemet's Membrane

A more thorough understanding of corneal aging and its relationship to systemic disease and exogenous factors should result from detailed study of morphologic, physiologic, and biochemical functions of normal and diseased cells in numerous stages of development and under various stressful circumstances.

Practical clinical information on endothelial decompensation caused by drugs and surgery would permit a more rational approach when subjecting a stressed, aged cornea to intraocular surgery. In addition, useful information on corneal alterations caused by systemic diseases could also be obtained.

Classical Genetic Studies of Myopia and Hereditary Corneal Diseases

Research on hereditary corneal disease is facilitated by the cornea's easy accessibility to in vivo examination and the availability of corneal biopsy and autopsy material. Means for the tissue culture of corneal cells are well-established. Because developmental disorders of the cornea constitute a significant part of clinical practice, the identification of conditions with a genetic basis can permit the recognition of those at high risk to such disorders among the close relatives of patients being treated.

Thus, classic genetic analyses of anterior segment malformation, Fuchs' dystrophy, keratoconus, and myopia are recommended.

Only a few investigators are presently working on the delineation of hereditary eye diseases; further training in this area is desirable.

5

Corneal Transplantation and Stromal Injury and Repair

RESEARCH IN THE entire subprogram, *Corneal Transplantation and Stromal Injury and Repair*, is considered by the Panel to be of the highest priority.

Corneal Transplantation

Approximately 10,000 corneal transplants are performed each year in the United States. This is an operation which can visually rehabilitate someone who is blind from corneal disease. Those afflicted are often young, sometimes only infants. The potential social and economic saving afforded by this procedure is surely worth a relatively modest research investment.

In addition to the beneficial effects of corneal transplantation, the cornea represents a somewhat simplified anatomical system of significant importance to general medicine, particularly with respect to immunological study. It provides an ideal study model because there are no blood vessels in the cornea, it is accessible to sampling and therapeutic agents, and the second eye can be used as a control. The corneal stroma is relatively acellular, and it is easy for immunological reactions to be studied on a single cell basis and for graft reactions to be quantified. Thus, corneal transplants are an ideal structure for studying, for example, tissue typing. The relatively mild reaction of the body to corneal transplantation may help in identifying possibilities for therapy which are overlooked during massive reactions to kidney or heart transplants.

Stromal Injury and Repair

All major infections and chemical and mechanical trauma of the cornea heal with the production of opacities which impair vision. Lesions of the cornea account for approximately 6 percent of all blindness or about 30,000 cases of blindness annually in the United States alone. Trauma, especially in children, often causes serious visual impairment which leads to significant social and economic problems for the child and his family. A long-term objective of research in this area is to modify the healing process to produce a less opaque and mechanically stronger tissue.

Although it is very tempting to look at recent advances in understanding the transparency and opacity of corneal tissue and promise imminent breakthroughs if only sufficient support is given, research is not that simple or predictable a process. Nevertheless, one can be sure that without determination, concentration, and sufficient funding, vision science will not progress in this area. Progress will come from the careful accumulation of information concerning normal corneal tissue and its healing processes.

Accomplishments

Corneal Transplantation

One of the primary reasons this Panel chose corneal transplantation as a priority area for NEI-supported research is that recent progress has been rapid and that further progress can be expected with a small investment of funds and manpower. Findings in this area can serve as an important model and source of information to the transplant field as a whole.

The specular microscope now enables scientists to examine corneal tissue more thoroughly before it is used as a graft.[41] This procedure, as it is now developing, may greatly increase the success of corneal grafts by reducing the amount of primary tissue failure. However, further developmental work is necessary.

Eye banking has involved taking the eye of the donor after death and simply putting it in a refrigerator. The new procedure of removing the corneal tissue which is to be used for transplantation and placing it in a nutritive medium (M-K media) has revolutionized corneal transplantation.[42] It also appears to have dramatically decreased the number of primary tissue failures and permitted the storage of corneal tissue for a longer period of time. As a result, surgeon, recipient and optimal tissue can now be brought together as needed. Work on corneal cryopreservation and tissue culture promises even longer storage of tissue and will facilitate tissue typing and other kinds of tissue matching. M-K media preservation and, to a lesser extent, cryopreservation are now in general use by many eye banks.

The primary cause of late graft failure is immune rejection. Many patients with chemical burns and badly vascularized corneas cannot be treated very successfully by corneal transplantation because of the graft's rejection by the patient's immune system. Two very promising approaches have been developed for the prevention of graft rejection. One involves simply dipping the corneal tissue in blocking antibody.[43] In animals, this has been shown to prolong graft survival and decrease the incidence of rejection, but studies in humans have not yet been performed. HLA matching is also an extremely promising technique in which tissue is cross-matched with donor antigens. Preliminary studies in many patients have already shown that those who are antigenically compatible seem to be less susceptible to graft rejection.

Corneal Stromal Injury and Repair

The prospects of understanding, and of possibly controlling, the physical, chemical, and biological factors that cause the development of a weak, opaque cornea have been considerably increased by recent research developments. If healing could take place without opacification, much blindness could be prevented. Recent studies using the eye as a model have also demonstrated that tumors produce an angiogenesis factor that stimulates the formation of blood vessels in normal hosts. Furthermore, extracts of cartilage and other substances

may prevent this ingrowth of vessels. The possibility of preventing vessel ingrowth has profound implications in the eye for the treatment of diabetic retinopathy, for the prevention of corneal vascularization after injury, and of course, as a model for vascularization and tumor growth elsewhere in the body.

Current corneal transparency theory postulates restrictions in the dimensions of the cross-sectional diameter of collagen fibrils and interfibrillar spacing. These are believed to insure small distances between fluctuations in the refractive indices of the macromolecular constituents. Corneal transparency is therefore determined by the physical, chemical, and interacting properties of collagen and interfibrillar material, specifically glycoproteins and proteoglycans.

Corneal scar tissue is markedly inelastic and mechanically weaker than that of the normal cornea. These differences are due to changes in the organization of the collagen fibers and fibrils which in turn are due to the interaction between these macromolecules, the interfibrillar matrix, and the nature and quantities of collagen intermolecular crosslinks.

Recent studies have suggested that epithelial, stromal, and endothelial cells in the cornea contribute to the deposition of connective tissue macromolecules during scar formation. Each cell type has the capacity to synthesize a unique mixture of collagen, proteoglycans, and glycoproteins. Differences in the carbohydrate content of collagen correlate roughly with fibril diameter and are vital to normal stromal collagen production.

The discovery of a glycosylated, intermolecular crosslinking species of collagen in corneal scar tissue suggests that its presence may alter or reflect a change in the orientation of collagen molecules, and thus, the structure of the fibrils which are formed. Changes in the structure of collagen fibrils result in morphological and physiological changes in the tissue.

Studies of the progressive changes in the quality of glycosaminoglycans found in healing corneal wounds and observations demonstrating the influence of these polyanions on collagen fibrillogenesis in vitro suggest that corneal glycosaminoglycans play an important role in scar formation. Control of the type of glycosaminoglycans found in corneal tissue may influence the formation of normal corneal collagen fibrils. Various agents are known to alter the types of glycosaminoglycans synthesized by fibroblasts.

New technological procedures permit the isolation and identification of many stromal macromolecules on a microscale, allowing investigators to extend their studies to human specimens. Ultrastructural studies have utilized the latest advancements in tissue preparation and instrumentation to provide a more detailed description of the healing process.

New developments in cell culturing techniques, in understanding cell behavior, and in methods for studying macromolecules will permit analysis and characterization of extracellular macromolecules produced by well-defined cells growing in vitro. The biosynthetic and degradative pathways of connective tissue macromolecules and the mechanisms controlling the activities of these cells have been extensively studied. These approaches and techniques can now be applied to eye research. The recent discovery that collagenase enzymes may cause dissolution of stromal collagen and stromal ulceration has also been an important breakthrough.

Research Objectives

- Improve the already high success rate of corneal transplantation through techniques which help assure the optimal condition of the tissue to be grafted

- Increase understanding of the biochemical and structural basis of corneal opacification following injury
- Find means of interfering with these processes to prevent or reverse corneal scarring

Research Needs and Approaches

Corneal Transplantation

Specular microscopy needs to be developed into a simple and convenient procedure so that eye banks can routinely examine tissue to be certain that corneal cells, especially endothelial cells, are in optimal condition for corneal transplantation. This would include making sure not only that the cells are undamaged but that there are an adequate number of residual endothelial cells on the donor's tissue. The effort required for a project such as this would be modest.

The handling of tissue for corneal transplantation can be facilitated by improving the present M-K storage media and adapting knowledge gained through tissue culture to improved corneal storage. Better media, the flux of osmotically active agents across the endothelium, and different storage temperatures may all be important. For example, before nutritive solutions were available, it was essential to stop totally metabolism in the donor cornea, a detrement to preservation. Now that nutritive solutions can be used, terminating metabolism in no longer necessary. Ideally, a method could be developed which requires little care and involves no great hazard to the tissue but which permits some metabolic function to take place.

At present, there are two major laboratories involved in such studies. A small increase in funding for another five years should be adequate to define ideal preservative techniques.

Basic investigations of blocking antibodies have already been performed in animals. What is required now is a multi-institutional trial of blocking antibodies in humans. This would involve the simple preparation of antibody into which the cornea would be dipped before it is transplanted. The risks to the patient should be negligible and the potential benefits great. To test its value adequately, such a trial would require the efforts of several clinical investigators and cellular immunologists for a period of about five years.

The role of HLA typing and HLA cross-matching should also be investigated. Transplantation antigen studies would require one or more corneal antigen typing centers. Study of an adequate number of patients would require funding for approximately five years.

Corneal Stromal Injury and Repair

Four major areas in need of additional research are:

- Biochemical characterization of the normal and scarred cornea
- Ultrastructural characterization of normal and scarred cornea
- Further study of the sources and methods of neutralizing collagenolytic enzymes
- Manipulation of biosynthetic and degradative pathways of corneal metabolism to control the interaction of collagen and interfibrillar materials

The experimental approach to corneal healing should involve analytical or chemical dissection to define earlier in the healing process the molecular organization of extracellular components and the relationships among these components. In addition, a biosynthetic or cellular approach is needed to define the behavior of connective tissue cells in culture and the factors affecting them. Because it will encompass biosynthesis, maturation, and remodeling of scar tissue, this combined approach should help define the interaction between cells and extracellular material in corneal scars.

Further biochemical work needs to be undertaken to determine with greater certainty the source of collagenase enzymes and the triggers for their elaboration, the biochemical properties of these enzymes, and the pharmacological methods for their inhibition. Proper definition of these enzymes and their properties will be clinically useful in helping to prevent corneal stromal ulceration. In addition, further work needs to be undertaken on purifying and sufficiently inhibiting the enzymes in order to prevent corneal scarring. Studies with angiogenesis inhibitors should be performed to prevent corneal vascularization.

At present, the National Eye Institute funds approximately $400,000 each year in grants on stromal biochemistry and development, collagenase, and collagenase inhibition. This level should certainly be maintained, but it is not certain that increased funding is necessary at this time.

In particular, such research should aim to:

- Investigate the biochemical characteristics and interacting properties of the structural macromolecules of the normal cornea
- Investigate alterations in these macromolecules and the changes in their relationships within the corneal scar
- Provide definitive ultrastructural information on corneal healing in order to determine which cell types are responsible for the deposition of scar tissue and to define the architecture of the scar
- Establish cell lines in culture from normal and scarred corneal tissue
- Utilize the cell lines to isolate and characterize normal and scar procollagens, proteoglycan complexes, and glycoproteins, and determine the specific relationships between macromolecular products
- Utilize these cell lines to test the effects of various pharmacological agents on the biosynthesis of scar components as a model for manipulating the healing processes

Such study of corneal stromal injury and repair is probably best performed by teams which include a biochemist who is familiar with collagen synthesis and ground substance matrices and skilled at tissue culture, a morphologist, and a clinical scientist.

Priorities and Recommendations

Corneal Transplantation

- Improve specular microscopy so that it is simple and convenient for eye banks to examine tissue routinely for its suitability for corneal transplantation.

- Improve M-K media by applying the latest advances in tissue culture techniques.
- Perform a study of blocking antibodies in humans to see whether dipping the cornea in such antibody before transplantation can prevent immune reactions.
- Investigate transplantation antigens, the role of HLA typing, and HLA cross-matching.
- Determine with greater certainty the source of collagenolytic enzymes, their biochemical properties, pharmacological inhibitors, and also how to purify such proteins. Study use of angiogenesis inhibitors to prevent corneal vascularization.

Corneal Stromal Injury and Repair

- Compare the biochemical and ultrastructural characteristics and interacting properties of the structural macromolecules of the normal and scarred cornea.
- Find pharmacological means of manipulating the biosynthetic and degradative pathways of corneal metabolism in order to control the interaction of collagen and interfibrillar materials as a means of preventing or reversing scarring.

Resource Requirements

In fiscal year 1977, the NEI will fund approximately 13 research grants and one research contract in this subprogram. The Panel recommends an additional nine research grants and one specialized clinical research center grant, bringing total NEI funding of *Corneal Transplantation and Stromal Injury and Repair* to $1,875,000. The tables at the end of this report include a list of recommended new projects.

6

Tumors and Other Lid, Conjunctival, and Orbital Problems

ALTHOUGH LID, ADNEXAL, and general orbital problems other than those which are considered in this report are common and although research on their treatment is important, further advances against them are expected to result from scientific and medical disciplines other than vision and ophthalmology. Similarly, the diagnosis of orbital malignancies may be improved in part by new technical developments such as refinements by private industry of computerized axial tomography (CAT). It is the Panel's opinion that although this area has been relatively neglected and, therefore, some significant research effort is important and worthwhile, it is not one of the highest priority for NEI support in corneal disease research.

A great number of inflammatory and neoplastic lesions arise within the lids and orbit. Trauma and developmental abnormalities of the lids and orbit are significant ocular problems.

Pseudotumors and Lymphoma

Pseudotumors are a loosely defined but clinically important group of orbital inflammatory disorders. They occur without readily apparent cause and can create considerable visual morbidity. In general, little is gained by surgical intervention except for diagnostic purposes when the presence of a true neoplasm cannot be ruled out by other means. Not only does pseudotumor pose a diagnostic problem for the physician, but the pathologist also faces a dilemma in certain cases in distinguishing a pseudotumor with lymphocytic predominance from a true lymphoma with systemic and possibly lethal implications.

Tumors of the Lids—Basal Cell Carcinomas

Basal cell carcinomas are the most common cancer of the eyelid, the site of 80 percent of all facial cell tumors. Basal cell tumors at the medial canthus also present special problems in management. Since basal cell carcinoma of the lid is related to exposure to sunlight as well as to race, it represents an interesting model of an environmentally induced tumor with a genetically determined component.

Malignant Melanoma

Malignant melanoma arising from acquired melanosis of the conjunctiva is a particularly important condition in ophthalmology. In the past ten years or so, the treatment for this condition has undergone change from wide extirpative surgery to local resection. Although not a common lesion, it is one which has distinctive characteristics. Study of its features may lead to better understanding of its nature and provide a rational basis for its treatment.

Orbital Tumors

Pathological processes that involve the orbit may arise either from soft tissues within the orbit or by invasion of the orbit from an adjacent cranial fossa or paranasal sinus. As a result, the globe may be displaced or proptosed, and the function of the optic nerve, extraocular muscles, and globe may be disturbed.

When a tumor invades the orbit from an adjoining area, the bone is usually destroyed at the site of tumor entry. This bone destruction may be recognized on plain films or by tomographic roentgen ray studies, and the presence of a tumor can be inferred.

A pathological process which arises from soft tissue within the orbit usually produces no changes in the bone structure. Thus, many tumors of varying malignant potential arise from the orbital soft tissues, yet cause no change in the bony wall of the orbit.

Accomplishments

Pseudotumors and Lymphoma

Advances in endocrinology are slowly elucidating the mechanism of orbital infiltration after pituitary-thyroid abnormalities, and newer surgical techniques can correct the proptosis and stare, but basic mechanisms remain uncertain.

Tumors of the Lids—Basal Cell Carcinomas

Research on the problem has been limited to histological descriptions and attempts to improve tumor management. The occurrence of marked lymphocyte infiltration of the tumor following chemotherapy with trichloracetic acid suggests an immune response in this highly successful procedure which has a cure rate greater than 99 percent.

Orbital Tumors

Significant advances in analyzing orbital soft tissues have been made in the past 20 years by special radiographic methods and ultrasonography. Arteriography, phlebography, and orbitography have been the subject of exhaustive studies which have made their limitations well known. Refinements may be expected, however, from isometric displays and computer analysis of ultrasonic scans.

The most recent advance in studying orbital soft tissues is the CAT scanner, a device which has revolutionized the approach to analyzing orbital structures and has significantly improved the clinician's ability to recognize a wide variety of orbital abnormalities. However, significant problems still exist with using this new method. These are largely due to the small size of the orbital structures and the fact that these structures have a specialized anatomy that is constantly in

motion because of normal eye and muscle movement. There is, however, significant potential to improve the image of ocular and orbital structures formed by CAT scans.

Research Objectives

- Improve means of diagnosing corneal pseudotumors and lymphoma
- Investigate the epidemiology of basal cell carcinomas of the lids
- Improve therapy of malignant melanoma
- Develop improved instrumentation for diagnosing and visualizing tumors of the orbit

Research Needs and Approaches

Pseudotumors and Lymphoma

Newer diagnostic modalities—such as computerized axial tomography, computerized ultrasonography, and radionuclide scanning—are valuable research tools that ideally can be improved to a level of diagnostic accuracy which will render biopsy unnecessary.

Immunoglobulin studies directed at the discovery of surface markers for the identification of B and T lymphocytes hold promise in characterizing these lesions.

Prospective studies involving a ten-year follow-up of patients diagnosed as having pseudotumors or lymphoma are necessary in order to establish the natural history of these diseases and to settle the questions of whether pseudotumors ever evolve into lymphoma and whether lymphoma ever begins in the orbit and then metastasizes at a later time. Elaborate research protocols will be essential to any long-term study of this disorder.

Tumors of the Lids—Basal Cell Carcinomas

The apparent relationship of sunlight exposure to basal cell carcinomas presents a clear opportunity for study of an environmentally caused tumor. Although the number of people exposed to long periods of sunlight because of their occupation may be decreasing, there are now many more people exposed as a result of outdoor recreation and sunbathing. Because basal cell carcinomas of the eyelid are treated by a relatively small number of ophthalmologists, dermatologists, and plastic surgeons, patient data should be readily available for study.

Research studies with high possible yield in this area include:

- Study of the incidence of eyelid basal cell carcinomas in different geographic areas of the United States by age, sex, race, occupation, and amount of actinic exposure
- If areas of high incidence are identified, a prospective study to look for continuing trends should be instituted
- Based on these data, opportunities should be explored for dealing with this problem in high-incidence geographical areas

Malignant Melanoma

Protocols for clinical studies of the stages, therapy, and follow-up of malignant melanoma will have to be developed and will probably be best prepared through a collaborative effort among three or more institutions. Studies of cellular immunity may be performed with fewer patients in single institutions.

Orbital Tumors

The development of improved computer technology for use in accurately and precisely diagnosing orbital tumors remains an ideal which could eliminate the need for surgery in many cases. Recognition of all swollen extraocular muscles, pseudotumors, and benign lesions could then be expected. An improved CAT scan for the orbit would serve as an archetype for application to other small structures. Development of a machine of this type by private industry should be encouraged.

Significant improvement in the diagnosis of orbital and lacrimal pathology would occur if it were possible to visualize directly the antrum, orbit, and lacrimal sac and duct. This important breakthrough could be accomplished with currently available, specialized fiberoptic probes. Although these special probes have not been used by ophthalmologists in any detailed studies to evaluate their potential value, such tools could be tremendously useful. Not only could they be used for direct visualization, but also for performing biopsies and for photographically recording what is viewed.

The equipment needed to develop these optical miniprobes is relatively inexpensive and could save many patients extended hospitalizations and surgery. Funding in this area would stimulate the use of available equipment and the development of new, specialized probes which could serve the particular needs of ophthalmologists in orbitoscopy, antroscopy, and dacryocystoscopy.

Recommendations

Pseudotumors and Lymphoma

- Establish appropriate diagnostic protocols for patients with orbital lymphoma

Tumors of the Lids—Basal Cell Carcinomas

- Determine the role of environmental factors in the etiology of basal cell carcinoma of the eyelids

Resource Requirements

In fiscal year 1977, the NEI will not fund any research projects in this subprogram. For FY 1978, the Panel recommends two new research grants for a total funding of $148,000 for *Tumors and Other Lid, Conjunctival, and Orbital Problems.* For a list of recommended projects, see the tables at the end of this report.

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Project and Resource Tables

Table 1: Corneal Diseases
Total Resource Requirements by Mechanism FY 1978

(Dollars in thousands)

	Research Grants		Specialized Clinical Research Centers		Contracts		Core Centers		Research Career Awards		Research Training		Total
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	Amt.
Estimated Support FY 1977	84	$ 5,439	2	$ 401	1	$28	3	$548	4	$100	51	$1,070	$ 7,586
Additional Requirements FY 1978	62	4,640	2	710	0	0	3	110	5	135	16	240	5,835
Estimated Total Support FY 1978	146	$10,079	4	$1,111	1	$28	6	$658	9	$235	67	$1,310	$13,421

Table 2: Summary of Recommendations by Subprogram

	Estimated Support FY 1977				Additional Requirements FY 1978				Estimated Total Support FY 1978			
	Number of Projects				Number of Projects				Number of Projects			
Subprogram	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)
1. External Ocular Infections and Inflammatory Diseases	32	1	0	$2,413	18	1	0	$1,703	50	2	0	$ 4,116
2. Dry Eyes and Tear Abnormalities, Epithelial Disorders, and Drug Delivery	8	1	0	591	17	0	0	1,273	25	1	0	1,864
3. Refractive Problems and Contact Lenses	0*	0	0	0	8	0	0	599	8	0	0	599
4. Corneal Edema, Dystrophies, and Inherited Disorders	31	0	0	2,017	8	0	0	599	39	0	0	2,616
5. Corneal Transplantation and Corneal Stromal Injury and Repair	13	0	1	847	9	1	0	1,028	22	1	1	1,875
6. Tumors and Other Lid, Conjunctival, and Ortibal Problems	0	0	0	0	2	0	0	148	2	0	0	148
Other**				1,718				485				2,203
TOTAL: *Corneal Diseases*	84	2	1	$7,586	62	2	0	$5,835	146	4	1	$13,421

*There is one research project grant involving orthokeratology now supported in the *Sensory and Motor Disorders of Vision* program.
**Core Centers, Research Career Awards, and Research Training

Note: The three project and resource tables are explained in the introduction to this volume.

Table 3: Recommendations by Subprogram

Chapter 1: External Ocular Infections and Inflammatory Diseases

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Herpes Simplex			
1. Determine the roles of live herpes simplex virus and its antigenic products (F, CR)	2	1 project	
2. Determine the host inflammatory response to herpes simplex viral infection and determine those host factors responsible for its recurrence (CR)	5	1 project	
3. Determine the neuronal factors responsible for: a. Viral latency and reactivation b. Pathways of viral transmission for interaction with ganglia c. Mechanisms which trigger viral shedding (F, CR)	4	1 project	1
4. Develop effective methods of herpes simplex viral therapy through elimination of the virus from its target organ and the neuronal reservoir by use of agents administered by multiple routes (F, CR)	3	1 project	
5. Modify host response by: a. Understanding neuronal and cell-mediated immunity b. Preventing harmful sequelae of inflammation (CR)	4	1 project	
TOTAL: *External Ocular Infections and Inflammatory Diseases*	18	1 (including 5 projects)	0

(Estimated Number of New Principal Investigators Required, FY 1978-80: 28)

Key:
F — Fundamental Research
CR — Clinical Research
CT — Clinical Trial
RD — Resource Development

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Dry Eyes and Tear Abnormalities (CR)			
1. Determine the composition and biophysical characterization of individual glandular secretions in corneal health and disease			
2. Describe immune mechanisms in lacrimal gland dysfunction			
3. Study tear flow and drainage problems and the control of normal tear secretion			
4. Study physicochemical stability of the tear film and how this is affected by environmental and emotional factors and drugs	5		
5. Study blink mechanisms and blink stimulation			
6. Analyze specific proteins in the tears in eye diseases			
7. Improve the clinical diagnosis of tear-deficient states			
8. Develop a means to diagnose systemic diseases from tear analysis			
B. Epithelial Disorders and Surface Injuries (CR)			
1. Study the adhesion between the epithelium and underlying tissue			
2. Search for epithelial growth stimulators	7		
3. Find means of ameliorating chronically inflamed epithelium			
4. Prevent destructive effects of epithelial opacity and vascularization on the stroma			
C. Drug Delivery (CR)			
1. Develop, evaluate, and compare new and existing means of drug delivery			
2. Study the pharmacokinetics of drugs used in and on the eye	5		
3. Determine genetic influence on drug reactions			
TOTAL: *Dry Eyes and Tear Abnormalities, Epithelial Disorders, and Drug Delivery*	17	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 26)			

Chapter 3: Refractive Problems and Contact Lenses

Recommendation	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Continuous-Wear Contact Lenses and New Contact Lens Materials			
1. Determine effects of new contact lens materials upon corneal physiology and metabolism and discover the cause of superficial vascularization from extended wear (F, CR)	3		
2. Establish criteria for the safety, efficacy, and uses of new lens materials (CR)			
3. Study corneal metabolism, hydration, and physiology in patients wearing contact lenses continuously, and improve instrumentation used to evaluate lens geometry, edging, bevels, and design (CR)	3		
B. Orthokeratology (CR)			
1. Determine the extent and duration of correction obtained by orthokeratology and the risks involved in the procedure	2		
TOTAL: *Refractive Problems and Contact Lenses*	8	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 13)			

Chapter 4: Corneal Edema, Dystrophies, and Inherited Disorders

Recommendation	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Corneal Edema, Dystrophies, and Inherited Disorders			
1. Determine a. Endothelial regeneration capacity b. Effects of different surgical and transplantation procedures upon the endothelium c. Characteristics of endothelial diseases d. Effects on the endothelium of various drugs e. Effects of different methods of corneal preservation (F, CR)			
2. Utilize new information on the endothelial pump to explore further its function, and study the effect of drugs on corneal hydration (F)	7		
3. Improve the design and instrumentation of clinical endothelial examination techniques (CR, RD)			
4. Establish the limitations of specular microscopy and fluorophotometry in determining corneal morphological and functional changes (CR, RD)			
5. Study the possible repopulation of the endothelium as an alternative to keratoplasty (F, CR)			
6. Develop routine procedures for gathering objective data such as endothelial population density in order to help the ocular surgeon decide if an operation will be tolerated and which surgical technique should be used (CR)	1		
TOTAL: *Corneal Edema, Dystrophies, and Inherited Disorders*	8	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 11)			

Chapter 5: Corneal Transplantation and Corneal Stromal Injury and Repair

Recommendation	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Corneal Transplantation			
1. Improve specular microscopy (RD, CR)	2	1 project	
2. Improve M-K media (F, CR)		1 project	
3. Study whether blocking antibodies can improve the outcome of corneal transplantation in humans (CT)	2	1 project	
4. Investigate transplantation antigens, the role of HLA typing, and HLA cross-matching (F, CR)		1 project 1	
5. Study collagenolytic enzymes and the use of angiogenesis inhibitors to prevent corneal vascularization (F, CR)	2	1 project	
B. Corneal Stromal Injury and Repair			
1. Study structural macromolecules of the normal and scarred cornea (F)	3		
2. Find pharmacological means of manipulating the biosynthetic and degradative pathways of corneal metabolism (F)			
TOTAL: *Corneal Transplantation and Corneal Stromal Injury and Repair*	9	1 (including 5 projects)	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 20)			

Chapter 6: Tumors and Other Lid, Conjunctival, and Orbital Problems

Recommendation	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Pseudotumors and Lymphoma			
1. Establish appropriate diagnostic protocols for patients with orbital lymphoma (CR)	1		
B. Tumors of the Lids — Basal Cell Carcinomas			
1. Determine the role of environmental factors in the etiology of basal cell carcinoma of the eyelids (CR)	1		
TOTAL: *Tumors and Other Lid, Conjunctival, and Orbital Problems*	2	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 2)			

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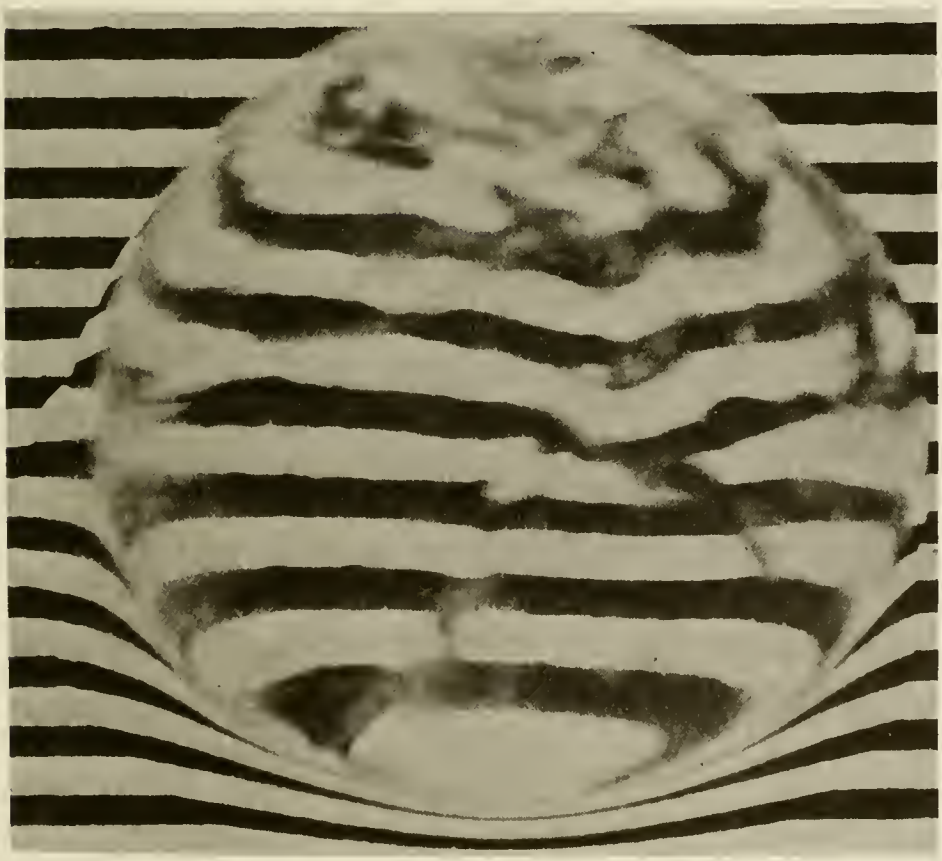
Cataract



Overleaf: Early human cataract. This photograph of a semi-opaque lens, which shows distortions of gradient lines placed behind the lens, is used to grade the density of the cataract.

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Foreword

THIS REPORT UPDATES and augments the discussion of cataract research in the 1975 report of the National Advisory Eye Council (NAEC), *Vision Research Program Planning*.

Members of the NAEC Program Planning Subcommittee's *Cataract* Panel reviewed the National Eye Institute's program of research in this disease. As a result of its analysis of the current programs and identification of the most important areas of cataract research today, the Panel has revised and expanded the cataract subprogram classification used in the previous report. The Panel believes that this new categorization more accurately reflects the breadth of knowledge in the cataract field, particularly the importance of research in genetic and drug-induced disease. In addition, a more specific delineation of subprograms better identifies the problem areas and may help to attract researchers from other areas of medicine to cataract research. The following is the classification of cataract subprograms used in this report:

1. The Normal Lens
2. Senile or Degenerative Cataract
3. Diabetic Cataract
4. Congenital, Metabolic, and Genetic Cataracts
5. Cataract Induced by Drugs and Radiation and Occurring Secondary to Other Eye Disorders
6. Dislocated Lens
7. Accommodation and Optical Problems of Cataract and Aphakia

Introduction

A CATARACT IS an opacity or group of opacities in the crystalline lens of the eye which can interfere with the passage of light through the eye and cause visual impairment. The major types of cataract are senile, occurring in the elderly; traumatic, resulting from accidents; drug-induced, from the toxic effects of drugs administered to treat ocular or systemic disorders; radiation, from the harmful effects of environmental or therapeutic radiation; congenital and/or genetic, occurring as birth defects; and secondary cataract, a complication of other eye disorders, conditions, or injuries.

The primary way to treat cataract is surgery which consists of removal of the opaque lens. To lessen optical disability subsequent to cataract removal, the patient must be fitted with eyeglasses, contact lenses, or an intraocular plastic lens implant. Drugs and diet, used to control blood sugar levels, can reverse cataracts due to disorders of blood sugar metabolism in diabetic patients.

In an effort to determine the causes of cataract and hasten the day when medical treatment can be used to treat or prevent cataract, the NEI supports investigators who study the normal lens and natural and experimental cataracts, seeking clues to the origin, mechanisms of formation, and improved treatment of this disease.

Importance

Cataract accounts for approximately one-sixth of all cases of visual impairment in the United States. Even though there are approximately 300,000 operations to remove cataracts each year, there are still an estimated 1,670,000 Americans who have trouble seeing with one or both eyes even when wearing glasses because of developing cataract. Of these, about 183,000 Americans six years of age or older, are unable to read newspaper print because of unoperated cataracts. And, of these, 64,000 Americans are blind—10,000 since birth—because of cataract.[1]

As is true of almost all other eye diseases, the major impact of cataract is not death but physical limitation, psychological suffering, and financial burden. During cataract development, a process which may take many years, vision becomes progressively impaired, often to a serious degree, i.e. legal blindness. During 1972, there were 283,000 discharges from short-stay hospitals for which cataract was the primary diagnosis. These accounted for more than one-half of all hospitalizations caused by eye disorders. Moreover, from April 1973 through April 1974, cataract necessitated 2,723,000 visits to physicians.[1]

Accomplishments

During the last ten years, NEI-supported investigators have been able to clarify the formation of cataracts produced by diabetes,[2] galactosemia[2,3] (a genetic error of metabolism), and rubella virus.[4] Moreover, certain cataracts of previously unknown origin are now known to result from chromosomal abnormalities that may either be inherited or occur during gestation.[5]

Investigators have also clarified how drugs (e.g. systemic corticosteroids) can cause cataract. This knowledge has resulted in more accurate calculations of corticosteroid doses administered to patients, and a greater awareness of the toxic effects of corticosteroids on the lens.

Studies of drugs in laboratory animals have demonstrated their toxic effects on the lens and their role in cataract formation.[6] These studies have served to warn the scientific community and federal agencies of their potential hazard to humans, and their use has been curtailed.

The NEI supports high-caliber laboratory scientists in studies investigating how the lens normally remains transparent or becomes cataractous.[7] Some of the normal functions of the crystalline lens and the genetic factors controlling its development have been explained. These studies employ, among others, the tools of electron microscopy, x-ray diffraction, computerized measurement of transport functions, and mass spectrometry.[8-11]

Surgeons have developed new techniques for cataract extraction and have improved upon established methods. One such innovation involves the removal of cataracts by sophisticated ultrasonic devices. The results obtained with these newer methods for cataract surgery are being compared with those of using traditional procedures for cataract removal.[12,13] In addition, the effects on the transparency of human and animal corneas of ultrasonics and of the several types of intraocular infusing solutions used in extracapsular cataract surgery and vitrectomy are being determined.[14,15]

Methods for correcting optical disturbances that ensue cataract surgery are receiving greater attention. Various types of continuous-wear contact lenses and improved intraocular lenses are being tested to determine their effectiveness in the correction of aphakia.[16,17] National clinical collaborative studies on the proper use and application of these devices are in the planning stage: preliminary meetings have been held, and opinions are being sought from practicing ophthalmologists and research scientists.

Cataract which develops as a complication of other ocular diseases, such as diabetes, galactosemia, uveitis, corneal inflammation, and retinitis pigmentosa, can augment an individual's existing visual problems. During the last few years, NEI-supported investigators have identified the cause of cataract in diabetes,[2] galactosemia,[3] and hypoglycemia[18] and are attempting to modify their course with drugs.[19] Other groups have clarified the mechanism for cataract formation in uveitis and for cataract development as a complication of corneal inflammation and retinal degeneration and are now studying their prevention.[20] Collaboration has increased and must develop further among cataract investigators and those working on other related eye disorders.

Goals of Cataract Research

Cataract extraction is one of the most successful of all major surgical procedures. Although NIH-supported research has contributed significantly to the advancement and perfection of modern surgical techniques, support for some

of the most recent developments in cataract extraction has come almost exclusively from cataract surgeons themselves and from corporations and other organizations in the private sector. Because of economic incentives, it is certain that industry will continue to support research and development in this area, and for this reason, the *Cataract* Panel recommends that the National Advisory Eye Council and the National Eye Institute continue to place primary emphasis on supporting research toward the *prevention* of this disease. The NEI should, however, be very concerned with the safety and efficacy of new surgical techniques as they are developed and take the lead in encouraging, organizing, and/or sponsoring clinical trials and other types of applied evaluative research at the appropriate stage in the development of these techniques.

In view of the foregoing, the major goals of the NEI *Cataract* research program are to:

- Determine the causes of cataract
- Find means of preventing or slowing cataract development
- Prevent development of amblyopia in children with cataract
- Devise new methods for correcting optical problems that follow cataract surgery
- Evaluate the safety and efficacy of new methods of cataract extraction
- Improve the quality of life and adaptation to new spatial relationships of patients who have undergone cataract surgery

Summary of Recommendations

THE CATARACT PANEL'S specific recommendations for research emphasis in each *Cataract* subprogram are provided in subsequent chapters. The following is a summary of those recommendations:

1. Perform biochemical studies of the animal lens and its zonules—especially of regulatory enzyme reactions, protein organization and structure, transport mechanisms and membrane chemistry, synthesis of glutathione and peptides, and lipid and carbohydrate metabolism.
2. Determine the chemical composition of the normal human lens and develop methods for culturing lens cells and for studying lens transparency.
3. Develop and apply new techniques for studying the embryology, morphology, and chemical structure of lens fibers and zonules.
4. Develop and apply new biochemical and biophysical techniques to the study of the normal senile lens and senile cataract.
5. Design photographic, television, and other electronic equipment for documenting changes that occur in the senile human lens and in cataract development.
6. Implant experimental intraocular lenses in animals and organize clinical trials of the safety and efficacy of intraocular lenses.
7. Conduct epidemiologic investigations into the nature and causes of senile cataracts.
8. Investigate further the chemical pathways involved in diabetic cataract and attempt to improve means of delaying diabetic cataract formation with drugs or chemicals.
9. Study chromosomal characteristics in animals and humans with cataracts and determine the role of inborn errors of metabolism in cataract formation.
10. Investigate the cataractogenic effects of viruses.
11. Investigate the effects of calcium ions on the normal lens and in hypoparathyroidism in humans and animals and study lens epithelial cells and fibers in tissue culture.

12. Determine the dose/response characteristics of cataract-inducing drugs in humans, laboratory animals, or in lens culture prior to administration to humans.

13. Determine the role of phospholipids in cataracts secondary to uveitis, inflammation, and retinitis pigmentosa.

14. Conduct controlled studies on the ocular effects of ultraviolet light in human populations and in laboratory animals.

15. Identify metabolic abnormalities in genetic disorders with dislocated lenses and study the effects of dislocated lenses on visual acuity.

16. Investigate the relationships between the ciliary body and the lens, particularly in relation to aging and presbyopia, and their effects upon the retina.

17. Attempt to optimize visual function in children with cataract both before and after surgery in order to reduce the risk of amblyopia, and, specifically, investigate the prevention of amblyopia in children by early surgery and the use of contact lenses and eyeglasses.

18. Establish a cooperative cataract research group to coordinate the activities of NEI-supported cataract researchers.

1

The Normal Lens

THE MAJOR ATTRIBUTE of the lens, its transparency, depends on the precise interaction of its differentiation and growth, its metabolism, and the preservation of its molecular structure. Gathering information on the normal lens, aqueous humor, and vitreous humor is prerequisite to interpretation of the alterations in these substances that take place during cataract formation. The uniqueness of the lens requires the search for and application of new technology to understand at the molecular level the normal lens and its derangement in cataract.

Information gained from these basic investigations, especially those involving laboratory animals, is already being applied to the study of the human lens and senile cataract. This includes knowledge of lens protein aggregation, lipid composition, changes in electrolytes, and small organic molecules in cataractous lenses. Successful detailed comparisons between normal and cataractous lenses are difficult because of limitations in obtaining normal human lenses for study. Yet, knowledge of the normal lens is essential to the understanding of senile cataract.

Studies using electron microscopy and electron histochemistry provide a better understanding of normal lens structure and function. The interdigitation between lens fibers and the lens sutures is dramatically revealed by scanning electron microscopy. Genetic codes governing lens fiber differentiation may be broken by investigations in epithelial cells and lens fibers grown in culture. Further, new enzyme and metabolic pathways are being studied in human and other mammalian lenses. Specific pathways for amino acids and glutathione transport and metabolism have only recently been shown to exist in the lens.

The lens is a unique tissue: it depends exclusively on its surrounding fluids for nutrition. Thus, studies of aqueous humor dynamics and composition relevant to glaucoma are also important to understanding how the lens environment affects its biological activities. The proteins of the lens are also unique because they are immunologically specific. The combination of biochemical, physicochemical, and immunochemical methods to study lens proteins is beginning to yield results. A comprehensive picture of the aggregation and disassociation process of lens proteins is emerging, and studies of the secondary and tertiary structure of lens proteins are being initiated. The membranes of the lens fibers are being separated, identified by electron microscopy, and analyzed chemically. Such studies provide a basis for understanding the transport of ions, amino acids, and sugars into the lens. It is now known that the lipid and carbohydrate composition of lens cell membranes is highly specialized. The chemical composition of the

zonules requires further study. Studies of the electrical gradients of the entire lens and electrical potentials of individual fibers indicate that electrical communication between lens fibers takes place in the normal lens.

Accomplishments

Transport

As a result of animal studies conducted by NEI-supported researchers on transport mechanisms in the lens, it is now known that amino acids, essential for protein synthesis, are obtained by the lens through carrier-mediated processes.[9,10] Recent studies have indicated that as lens epithelial cells differentiate into lens fibers during aging, the ability of the lens to accumulate amino acids is decreased. However, the factors responsible for aging, decreased ability to concentrate amino acids, and their relationship to cataract formation, if any, are not clearly understood. Further studies are therefore indicated. Similarly, the mechanism by which the lens maintains cation levels and thus regulates the hydration essential for its transparency, needs to be further scrutinized.

An interesting and potentially important development is the recent implication of glutathione in the transport of amino acids and cations. The lens contains an unusually high concentration of glutathione, and the transport process for both amino acids and cations is located in a single layer of epithelial cells across the anterior surface.[11] Reduction in the level of glutathione leads to a decrease in cation pumping activity and an increase in membrane permeability. Thus glutathione appears to have a regulatory role in cation transport and permeability in the lens. Loss of glutathione may be a factor in the accumulation of sodium and loss of potassium that contributes to the formation of various types of cataract. Since glutathione is present in most cell membranes, these hypotheses have general significance for biomedical research in general and need to be further tested.

Protein Chemistry

Considerable progress has been made in understanding lens proteins. The lens is composed of three major groups of soluble proteins—alpha, beta, gamma crystallin—and an insoluble protein fraction.[21] The primary structure of bovine gamma crystallin and of the polypeptide chains of alpha crystallin has been elucidated,[22] and beta crystallin is now under investigation.[23,24] The impact of aging upon post-translational changes of the human alpha crystallin macromolecule is now partially understood, and attention has turned to the effect of such changes upon the physical state of the protein and the development of cataract.[25]

Investigation of bovine alpha crystallin has demonstrated that with aging there is a shift from low molecular weight species of approximately 0.7×10^6 daltons to giant macromolecules ranging from 50×10^6 to more than 200×10^6 daltons. From light scattering theory, and studies of lens transparency, it is clear that such components can act as light scatter points and, when present in sufficient concentrations, cause opacification.[7] The transformation occurs only in the nuclear region of the lens and may explain the development of nuclear sclerosis and opacification.[26]

The situation in the human lens is similar although not clearly understood at present. With aging, there is an increase in high molecular weight (HMW) protein macromolecules, primarily in the central region of the lens. Studies indicate a

correlation between light scattering and the abundance of HMW species.[27] Recently methods have been developed for direct measurement of the size of the protein macromolecules in vivo, utilizing quasi-elastic light scattering and Raman spectroscopy.[28-30]

Elucidation of the mechanism by which the macromolecules are formed requires new information at several levels. It has been shown recently that the amino acid and polypeptide composition of HMW protein species are similar to the insoluble protein component of the lens. This fraction also increases with age and represents a considerable proportion of the total protein in the cataractous lens. It has been suggested that in the high molecular weight range, there is a broad spectrum of macromolecular sizes, extending from the so-called HMW protein to the insoluble components. It may be necessary to isolate and determine the structure of the polypeptide components comprising these protein species in order to characterize and relate them to the low molecular weight proteins found in the normal lens. Although normal human alpha crystallin has been well-characterized, little is known about beta and gamma crystallins in the human lens.

The changes in the protein polypeptide are in some cases quite marked, resulting in the appearance of dramatically smaller and larger polypeptides. Since protein synthesis is minimal in the central regions of the lens, such changes can only result from proteolysis or chemical cleavage of peptide bonds in the case of the smaller polypeptides, and the generation of cross-linked components in the case of the high molecular weight polypeptides.

Considerable attention has been directed to the yellow nontryptophan fluorescent components that appear to be associated with the high molecular weight and insoluble components and that may be involved in the cross-linking process and generation of these giant macromolecules.[31] Such fluorescent components may arise from photochemical reaction caused by near ultraviolet light. Very recently, some of these fluorescent components have been defined as beta carbolines and it has been suggested that they may act as cross-linking agents.[32]

Lens Embryology

Congenital cataracts can arise from genetic abnormalities. Genetic defects can also cause absence of the lens and anomalies of lens shape, size, or position. These cases result either because of disturbances in the execution of the genetic program for the establishment of the normal lens cell, because the program itself was defective, or because of external influences. For an understanding of these pathological conditions, a thorough knowledge of normal lens development is essential. Because of practical considerations, studies on human embryonic lenses are not commonplace and animal models must be used.

Considerable progress has been made in understanding lens development during the past decade. At the morphological level, several factors have been identified that may be involved in shaping the early lens rudiment, as well as in the later formation of lens fibers from the anterior epithelium.[33] Within the cells, organelles have been found—microtubules and microfilaments—which probably act as cytoskeleton and contractile elements, respectively. These structures may play a role in regulating the shape of lens cells. Cell replication may lead to cell crowding and so cause changes in the shape of the lens rudiment. Of considerable interest is the demonstration of an extracellular matrix between the future lens and the lens inducer, the optic vesicle.[8] The density of this matrix peaks just prior to the first signs of lens differentiation, suggesting that the synthesis of this matrix may play some role, as yet obscure, in the induction of lens differentiation.

Despite these findings, which need further expansion, many aspects of lens morphogenesis are still poorly understood. More studies are needed of early lens cells at the ultrastructural level, including scanning electron microscopic work and studies of cellular membranes and associated structure. The role of cell death in release of the lens rudiment from the remaining surface ectoderm deserves further consideration. Quantitative studies of the lens formation process are needed. It should also be emphasized that lens development and the development of the rest of the eye are closely intertwined; lens development, therefore, cannot be studied without consideration of the development of the eye as a whole.

Work of this nature can be expected to increase understanding of lens induction, which in turn may have implications far beyond the field of lens embryology and serve to expand general knowledge of embryonic differentiation.

Molecular Biology

The specific proteins of the lens, the crystallins, have received much attention from lens embryologists. It has been shown in the past decade that these proteins do not appear until lens formation is well under way and that their synthesis is unique for the lens cells. This is in contrast to the opinion widely held prior to the 1960's that crystallins are universally present throughout the very early embryo and gradually become restricted to the area of the eye and the lens. At the genetic level, this means that lens differentiation is now considered to involve the turning on of specific genes, whereas earlier theories held that a gradual restriction of lens-specific gene activity was responsible for lens formation. Recently developed techniques have made it possible to bring these investigations one step closer to the actual genes involved, by isolation of the messenger RNA molecules that code for the crystallins.[34] Based on the experiments with crystallins, the few studies done to date confirm these concepts. The very potent tools of modern molecular biology, utilized in combination with experimental embryology techniques, make possible expanded studies of lens cell differentiation and offer the exciting promise of better understanding of the control of individual gene activity.

Research Objectives

- Improve understanding of how the normal lens develops
- Elucidate the physicochemical mechanism underlying maintenance of lens transparency
- Demonstrate how disruption of normal physicochemical processes by prenatal or developmental influences, external factors, other ocular and systemic disorders, and aging can lead to cataract formation

Research Needs and Approaches

- Definition of transport mechanisms of electrolytes, carbohydrates, amino acids, and lipid molecules
- Determination of the chemical composition and metabolism of proteins, lipids, and carbohydrates in the normal human and animal lens

- Control of enzymatic pathways for synthesis and degradation of proteins, lipids, and carbohydrates
- Culture of normal human lens
- Characterization of the morphological organization of lens epithelium, lens fibers, and zonules by electron microscopy
- Determination of the electrical gradients of the entire lens and electrical potentials of individual lens fibers
- Definition of the synthesis of macromolecules and lens fiber differentiation in the embryonic lens
- Investigation of the function of intracellular lens organelles by electron histochemistry

Priorities and Recommendations

- Perform additional biochemical studies of regulatory enzyme reactions, protein organization and structure, transport mechanisms and membrane chemistry, synthesis of glutathione and peptides, and lipid and carbohydrate metabolism of the animal lens and its zonules
- Determine the chemical composition of the normal human lens including carbohydrates, lipids, proteins, and electrolytes
- Develop methods for culturing the human lens and lens cells
- Develop and apply new techniques for studying the embryology and morphology of lens fibers and zonules
- Apply new techniques for study of lens transparency and transmission of light by the lens

Resource Requirements

In FY 1977 the NEI will fund approximately 38 research grants and one specialized clinical research center grant in the subprogram *The Normal Lens.* Estimated FY 1977 funding will amount to $2,646,000. The Panel recommends an additional seven research grants for FY 1978, bringing total funding for research in this subprogram to $3,185,000. Specific recommendations and the required resources to implement them may be found in the tables at the end of this report.

2

Senile or Degenerative Cataract

LENS OPACITIES DEVELOP in the majority of the elderly. Their incidence increases progressively after age 50, and they are found in approximately 95 percent of the population age 85 or older.

The rate of development and morphologic type of senile or degenerative cataract varies considerably with the individual. This heterogeneity, for reasons unknown, accounts for the various types of senile cataract which produce either minor or major impairment of vision. The primary types of human cataract are:

- *Vacuoles* in the anterior cortex, posterior cortex, or lens equator. These vacuoles may vary in size, shape, and position. Small vacuoles present in the lens equator do not affect vision, whereas similar vacuoles in the anterior or posterior cortical area and near the visual axis can result in significant visual impairment. In senile cataract, the progression and spontaneous reversibility of cortical vacuoles has been documented, offering hope that the early stages of cataract development could be modified therapeutically if the pathogenesis were understood.

- *Cortical opacities* resulting in the majority of cases from some previous damage to the lens which had caused vacuoles in the lens cortex. Opacities which have not gone through the stage of lens vacuolation do exist. As with vacuoles, maximal visual impairment results from cortical lens opacities present in the visual axis.

- *Nuclear opacities* (nuclear sclerosis), the most common type of senile cataract, involve a slow, progressive change in the color of the lens nucleus. At the initial stages, nuclear sclerosis is characterized by a yellowing of the lens nucleus. Later, and in many cases simultaneously with the development of cortical vacuoles and opacities, the nucleus becomes yellow-brown to brown in color. These changes of the lens nucleus are accompanied by its gradual hardening. The brown or brunescent cataracts are harder than the yellow ones.

- *Mature cataract*, the total opacification of the lens. This is the end stage of the various types described above. Generally, the cortex of the cataract is white and liquefied, and release of lens protein into the aqueous humor and vitreous humor may occur. In the latter case, an inflammatory reaction to lens protein (lens-induced uveitis) may develop.

Senile cataracts can be removed surgically and optical rehabilitation provided.

In the United States, between 300,000 and 400,000 cataract operations are performed annually.[1] The actual incidence of visually disabling senile cataracts is probably four times this number, with the worldwide annual total estimated at 5 to 10 million new cases.

Accomplishments

The development of safe and effective methods for extracting senile cataract is one of the great achievements of modern medicine. Once accepted as a natural consequence of aging, senile cataract is today recognized as a disease which can usually be successfully treated and vision satisfactorily restored.

The development of new methods of cataract extraction, including ultrasonic liquefaction of the lens and its removal by suction through a hollow needle, and intraocular lens implantation, have been of great interest to both physicians and their patients. However, widespread publicity in the popular press and news media has tended to over-glamorize these techniques, stressing the technology and potential benefits, while largely ignoring the risks or contraindications. Unquestionably, these methods offer important advantages, but, without systematic, long-term, controlled studies, the magnitude of the attendant risks versus benefits may never be fully known.

Recent developments in objectifying the classification of cataract may provide the necessary tools for long-term documentation and statistical evaluation of the stages of senile cataract progression in entire populations, i.e. the natural history of the disease. Three groups of investigators have developed optical equipment for photographing and precisely measuring the size and density of cataracts.[29,35,36] This equipment provides permanent documentation of each cataract, which can later be compared and properly classified by independent observers.

A British investigator has developed a sophisticated system of slit lamp image photography which enables photographic enlargements to be made with a grid to demonstrate the overall shape of the lens and anterior chamber, the position of any opacity within the lens, and the radii of curvature of the lens surface. These photographs may be studied further with either a microscanning densitometer or a color TV density analyzer. From these studies, significant evaluations of the lens during accommodation and aging have been made.[36]

NEI-supported investigators have used a photographic method to test the theory that altered appearances in the lens may be due to a change of its light-scattering properties. The resulting negatives were subjected to a microdensitometric analysis.[29] However, the cortex proved difficult to study because of the large variety and positions of the opacities.

These technological developments could be further expanded by applying even more sophisticated image recording systems and computerized electronics.

Ideally, investigations of protein structure, transport characteristics, and other biochemical studies should be conducted in senile cataracts at various stages of development and correlated with morphological appearance. Furthermore, photographic documentation is needed for longitudinal studies in which the effect of environmental or nutritional factors on cataract formation could be properly assessed.

Causes and Pathogenesis

Senile cataracts develop during a span of from three to 20 years. Their causes are unknown but during aging, a series of metabolic changes are known to occur in the lens and in surrounding fluids which may contribute to cataract formation.

Environmental factors such as ultraviolet light may have a cumulative effect on the lens that eventually results in cataract formation, but this has not been proven. During the last few years, NEI-supported investigators have begun to gather information needed to determine which types of changes occur in the lens during senile cataract formation. These studies have revealed that in senile cataract there are abnormalities in proteins, membranes and their lipids, transport of electrolytes, and in advanced cataract, hydration. These abnormalities are discussed below.

Abnormalities in Lens Proteins

Proteins account for 33 percent of the weight of the normal human lens.[21] Thus, the lens contains a higher percentage of proteins than any other body tissue. Proteins, which are found inside the lens fibers, are arranged in such a way as to allow the passage of light through the lens. The physicochemical state and orderly arrangement of these proteins provide the lens with optical homogeneity and thus, transparency.[7] Protein organization depends on the orderly arrangement of amino acids and polypeptides into primary, secondary, and tertiary structures. Lens proteins are best studied by their separation into subclasses through such chemical procedures as ultracentrifugation, column chromatography, or electrophoresis, followed by determinations of amino acid composition or amino acid sequencing. The stereo configuration of lens proteins can be partially determined from their molecular weight. Small proteins can aggregate and become larger ones. It has been suggested that proteins of high molecular weight can scatter light and thus contribute to lens opacification.[7,20] Indeed, high molecular weight proteins (50×10^6 daltons) have been found in human senile cataracts.[37,38] Another mechanism for aggregation of lens protein may be the polymerization of lipids derived from lens membranes with protein molecules. This results in large protein-lipid complexes that are highly insoluble in water and may scatter light.[39]

Chemical dissection of lens protein can be performed by agents which split the bonds between protein molecules and between proteins and lipid molecules in lens fiber membranes. Figure 1 represents a gradient of lens protein solubility in water, urea, and guanidine from the weakest bonds (soluble in water) to the strongest bonds (soluble in NaOH or KOH).[40]

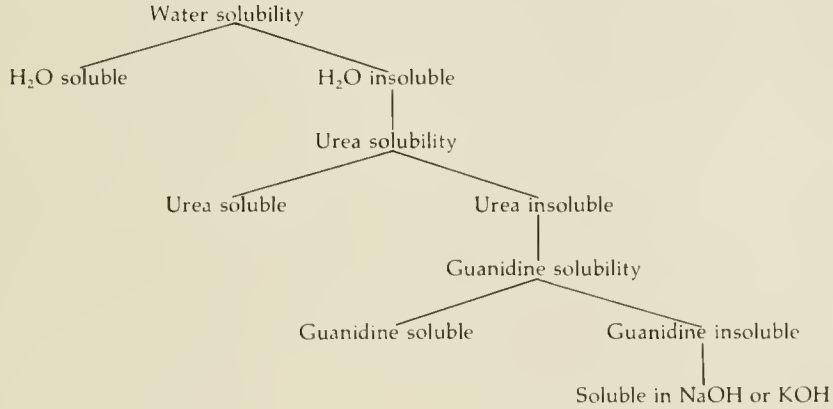

Figure 1. Solubility of lens proteins.

These techniques applied to studies of the proteins of the normal human lens and of senile cataract have yielded the following observations:

- *The concentration of proteins of senile cataract which cannot be solubilized by guanidine is higher than that found in the normal human senile lens.*[40] This finding indicates that

the bonds or attachments between proteins or between proteins and the lipids in membranes of lens fibers are strengthened in cataract. Strengthening of chemical bonds can result from changes in amino acid sequence or composition. Several investigators, however, have failed to find abnormalities in the amino acid composition of the urea-soluble, guanidine-soluble, or insoluble fractions of senile cataract.[41,42] Thus, other investigators have turned their attention to the tertiary and quaternary structure of cataract proteins, searching for abnormal patterns of organization, orientation, or amino acid sequence.

- *Aggregation of lens protein is abnormal in human senile cataract.* Aggregated proteins of high molecular weight are found in the normal senile lens, but are somewhat increased in senile cataract.[26,37,38,43] These investigations indicate that lens proteins suffer physicochemical or metabolic alterations during cataract formation. Furthermore, it has been postulated that Ca^{++} and/or water ionic changes in the lens microenvironment could cause or accelerate the process of protein aggregation.[44] As noted previously, large aggregates of lens proteins could cause lens opacification by scattering light and interfering with the optical homogeneity of the tissue.

- *Protein degradation is increased in senile cataract.* In the normal human lens, protein and polypeptide breakdown is slow and regulated by specific enzymes, proteases, and aminopeptidases. However, in senile cataract, this process appears to be accelerated.[45] The causes for increased protein degradation are not known, but several ions which can accelerate or decelerate the rate of protease activity may contribute to it.

Lens Membranes and Their Lipids, Lens Transport of Electrolytes, and Lens Dehydration

The water content of the lens is extremely low, and this state of relative dehydration maintains its optical homogeneity and transparency. Water, when present in excess, results in a cataract characterized by vacuoles and water clefts which scatter light and decrease vision. Thus, cataract prevention depends among other things upon the perfect functioning of lens water extrusion mechanisms.[46] In the normal lens, the preservation of lens dehydration results from the activities of cell membrane pumps which extrude Na^+ ions. The concentrations of Na^+, K^+, water, and Na^+K^+ATPase can be determined in the normal human and animal lens. However, in vitro studies of the rate of transport of these electrolytes in the normal human lens need to be performed. Lens cell membranes are made of various types of lipids, and modifications of their chemical composition affect the extrusion of Na^+ and water by the lens. The techniques for studies of lipids involve (a) separation by extraction with nonpolar solvents before and after degradation of the proteins, (b) determination of the various molecular subspecies in each lipid family (e.g. subclasses of cholesterols, sphingolipids, phospholipids, and neutral lipids) by thin-layer chromatography, and (c) analysis of their fatty acid composition by gas-liquid chromatography and mass spectrometry.[39,47]

These techniques applied to studies of human senile cataracts have yielded the following observations:

- *The chemical composition of lens membranes is abnormal in human senile cataracts.* Analysis of various lipid subclasses indicates that cholesterol and certain sphingomyelin and ceramide species are increased and their fatty acid content changed in senile cataract, compared to normal lenses.[39,48,49] Although cholesterol is synthesized by the animal lens and its concentration

increases with age in the human lens, the pathways for synthesis and degradation inside the human lens are not known. Increased cholesterol in human cataract may affect membrane permeability and compact or condense the proteins within the membranes. Further, the interaction of cholesterol with lens protein inside and outside the membranes remains to be determined.

- *The Na^+ content is increased and Na^+K^+ATPase activity is depressed in human senile cataract.* The Na^+ ion increases in senile cataract have been documented by three different laboratories.[50-53] Whether the increased Na^+ content of cataract is accompanied by water imbalance is not always readily apparent at the initial stages of cataract development. Although vacuoles in the lens cortex indicate retention of water, hardening and dehydration of the cataractous lens nucleus occur simultaneously. The water content of various parts of the lens during senile cataract formation needs to be measured. Similarly, depressed levels of Na^+K^+ATPase in senile cataract, reported by one laboratory,[54] need to be confirmed, and the nature of enzyme inhibition requires detailed study.

Treatment

Medical Treatment

There is no medical treatment for senile cataract. Once the basic mechanisms which lead to cataract formation are identified, a scientific approach to medical therapy can follow. Claims, based on laboratory experiments, which state that drugs or vitamins have a therapeutic effect on human cataract formation require accreditation by well-controlled prospective clinical trials.

Surgical Treatment

The only therapy available for senile cataract is surgery. The removal of a cataract from the eye is made by an incision in the cornea or sclera. The cataract is then either completely removed (intracapsular extraction) by grasping its capsule with forceps or by freezing it to a cold probe or by ultrasonic emulsification and suction (extracapsular extraction). Sutures close the surgical incision. Thanks to improved microsurgical techniques for intracapsular and extracapsular cataract extraction developed through research, patients are able to leave the hospital within a few days following surgery.[12]

After cataract extraction, the optical function of the natural lens must be provided by an artificial substitute, e.g. eyeglasses or contact lenses. Two types of contact lenses are used to compensate for absence of the lens (aphakia): hard or soft contact lenses which should be removed from the eye daily, and soft contact lenses which can be worn for days or weeks without being removed from the eye. (The latter type is currently available in the United States only for investigative purposes.) In the majority of patients, successful optical correction is achieved; however, a small number of patients notice distortions in the size or type of images when they use either glasses or contact lenses.

Plastic lenses placed within the eye at the time of surgery (intraocular lenses) have been developed over the past two and a half decades, mainly in the Netherlands, and are being used increasingly in the United States as an alternative for eyeglasses or contact lenses in the correction of aphakia.[10,55] Plastic lenses are made of polymethylmethacrylate and consist of a central optical portion for the passage of light, and a peripheral or haptic portion to allow lens

fixation to either the iris or the pupillary area. Because they replace the extracted natural lens in practically the same location, there are many optical advantages to intraocular lenses. The visual orientation of patients who have had an intraocular lens implanted can be excellent; however, certain complications of cataract surgery, such as corneal or macular edema, may appear more frequently in patients having received an intraocular lens implant.[55]

Approximately 10,000 to 20,000 intraocular lenses will be implanted during the coming year in the United States. The Food and Drug Administration has recently established guidelines to regulate the use of this device.[56] However, lack of controlled clinical trials and uncertainty over the long-term results of lens implantation make it too difficult to assess whether the ultimate benefits of this procedure outweigh the risks. Thus, a well-controlled clinical study of the safety, tolerance, and efficiency of intraocular lenses in humans is needed. In addition, some patients who have had cataract surgery previously have requested a "secondary" implantation of intraocular lenses. The surgical risk of lens implantation as a secondary procedure requires controlled evaluation.

Research Objectives

- Determine the causes and pathogenesis of senile cataract
- Develop means for objective classification and documentation of senile cataract
- Study the disease's natural history in representative populations
- Identify possible risk factors associated with senile cataract
- Evaluate the relative value of existing methods of senile cataract extraction and postoperative optical rehabilitation
- Find means of preventing or at least slowing the rate of development of senile cataract through drug treatment

Research Needs and Approaches

- Culture of human senile cataract in test tubes
- Determination of electrolyte, protein, sugar, and lipid composition and morphological abnormalities in the various types of senile cataract as compared to age-, sex-, and race-matched normal human lenses
- Classification of human senile cataract after documentation of morphological abnormalities by photography
- Comparison of chemical abnormalities of laboratory animal cataracts with those of human senile cataracts

Priorities and Recommendations

Causes and Pathogenesis

- Establish a cooperative cataract research group. Important advances toward the solution of the cataract problem may be

made by coordinating the activities of NEI-supported cataract researchers throughout the United States. The research data of this group would be sent to a coordinating center and disseminated to cooperating scientists. Periodic telephone conferences and meetings would be conducted to discuss data and arrange future experiments.

The immediate objective of the proposed collaborative effort would be to establish the various biochemical and biophysical characteristics of the normal human lens. The second objective would be to assess the significance of changes in these characteristics with respect to the etiology of cataract. Studies for establishing norms can be done in existing laboratories. However, before studies of cataractous lenses can begin, a standard classification of cataracts must be devised. A preliminary classification of various senile cataract subtypes has been designed so that comparisons of the results obtained in different laboratories will be meaningful.

The success of this program will depend upon the availability, collection, and distribution of normal and cataractous human lenses. A preliminary survey of potential cooperating institutions indicates that an adequate number of normal and cataractous lenses will be available. Although the main objective of the research group would be to obtain biochemical, morphological, and biophysical data on normal human lenses from eyes obtained from surgery, autopsy, or eye banks, attention should also be given to the cause of donor death. Such information should also be obtained in the study of cataractous lenses in order to gain additional knowledge of cataracts associated with systemic disorders.

Current research in humans and animal lenses on the metabolism of sugars, peptides, and fatty acids, on proteolysis and protein synthesis by the lens, and on lens transparency is providing basic information much needed by the cooperative group. Consequently, such basic studies represent the backbone of the research group and should be vigorously pursued.

- Develop and apply new biochemical and biophysical techniques to the study of the normal senile lens and senile cataract. Particular attention should be paid to those chemical compounds found in the senile lens and cataract whose metabolic pathways require further clarification, including lipids, carbohydrates, proteins, peptides, and electrolytes.

- Develop methods for culturing senile cataract.

- Design photographic, television, and other electronic equipment for documenting changes that occur in the senile human lens and in cataract development. More refined instrumentation and techniques for documentation of senile lens opacities are needed. Technological development in recording lens opacities may facilitate the determination of the natural history of cataract formation.

Treatment

- Organize large-scale clinical trials of the safety, tolerance, and efficiency of, and visual rehabilitation provided by, intraocular lenses, and of both continuous and intermittent use types of soft contact lenses used after cataract removal in humans.
- Study intraocular lenses in animals. Laboratory animals provide excellent models for testing the safety and tolerance of various polymethylmethacrylate lenses by the eye. Rabbit, dog, and cat lenses can be removed surgically, and specially designed intraocular plastic lenses can be implanted. The inflammatory reaction of the eye, the degree of corneal clarity and/or edema, the position of the plastic lens in the eye, the refractive state of the eye, and estimates of vision may all be determined from these animal studies. Moreover, better and more rapid procedures for the sterilization and preservation of plastic intraocular lenses can be determined by such experimentation.

Resource Requirements

In FY 1977 there will be approximately 20 research grants costing an estimated $1,313,000 in NEI funding for research in the subprogram *Senile or Degenerative Cataract*. The Panel recommends an additional 15 research grants and 13 research contracts for FY 1978. Estimated total funding for this subprogram in FY 1978 will be $3,468,000. See the tables at the end of this report for a list of recommended projects.

Appendix: Epidemiology of Senile Cataract

EPIDEMIOLOGY IS A quantitative, analytical discipline broadly concerned with the study of disease in groups of people. It is an approach well suited to assessing the magnitude of a problem, identifying possible etiologic factors, and determining the safety and efficacy of new preventive, diagnostic, and therapeutic maneuvers. Epidemiology is an effective tool for identifying conditions associated with the development of disease "risk factors." These are often the first important clues to etiology.

The many conditions known to cause cataract account for only a small proportion of the total problem. As yet there is no convincing explanation for the large group classified as senile or degenerative cataract. Unfortunately, senile cataract has received little epidemiologic attention in the past.

Accomplishments

One of the most promising areas of cataract research, and the one which has received the greatest epidemiologic attention, is diabetic cataract. The aldose reductase enzyme provides a ready explanation for galactosemic and classical diabetic cataracts. It may also account for senile cataracts among diabetics, and there is some epidemiologic data to support this hypothesis. If senile cataract is the result of abnormal carbohydrate metabolism, it should be far more prevalent among elderly diabetics than among the general population. The best available evidence is seemingly paradoxical: in the 52 to 64 age group, patients with cataracts have slightly elevated blood sugar levels;[57] but, a rather high number of patients with diabetes or abnormal blood sugar levels (10 to 15 percent) are found among those undergoing cataract surgery.[58] The current explanation for the paradox is that cataracts mature more quickly in people with diabetes than in the general population. But, another equally plausible explanation exists: diabetics are more likely to be seen by internists and referred to ophthalmologists and therefore more likely to have their cataracts identified and removed. Biochemical changes in the lens begin long before a cataract is clinically diagnosed. If the maturation process were accelerated, subclinical cataracts should become apparent earlier and the age-specific prevalence among diabetics increased.

From the epidemiologic viewpoint, most senile cataracts have diverse, perhaps compound causes which need to be identified. The extremely limited studies done

to date have already provided some promising leads. Investigators have demonstrated an inverse relationship between altitude and cataract prevalence in the Punjab, India,[59] despite the fact that potential exposure to ultraviolet light, a presumed risk, would be greater at high altitudes. This suggests that genetic or other environmental factors are of greater importance. However, dietary factors such as the mineral content of drinking water, quality and amount of food intake, and/or socioeconomic status could play a role in cataract formation in India.

Cataract prevalence in the Punjab, even in the least affected groups, is reportedly higher than that in Western India. Differences in methodology and definition make such comparisons hazardous, especially since the diagnostic reproducibility, even between investigators working together in the same institution, seems to differ by a factor of two. If substantiated, case control studies involving Indian villages of widely varying cataract prevalence, but limited differences in cultural and environmental factors, would likely lead to the rapid identification of possible high risk factors worthy of laboratory investigation.

In the United States, by adding ocular examinations to an ongoing comprehensive study of the incidence of cardiovascular and other diseases in a defined population in Framingham, Massachusetts, investigators have tapped a rich source of information at relatively little cost and effort. Preliminary analysis of their results indicates total serum phospholipids were increased in members of the study population with senile cataract.[57] If these findings are confirmed, they will provide an important "chemical handle" on senile cataract and stimulate further epidemiologic studies in other aging populations.

Research Objectives

- Identify populations with particularly high or low prevalence of cataract
- Identify possible risk or protective factors associated with high or low cataract prevalence
- Provide better data on the incidence of secondary problems caused by cataract and of the complications of cataract surgery

Research Needs and Approaches

Few of the attempts that have been made to measure the magnitude of the cataract problem are directly comparable: they differ in their analysis (incidence, the number of new cases in a community per year, and prevalence, the total number of cases present at any one time); methods of examination (hand lights, direct ophthalmoscopes, and slit lamps); definitions (any trace of cataractous change, cataracts producing some minimal reduction in visual acuity, and blindness); and samples (old age homes, blindness registries, selected communities, and randomized samples of the entire population).

At least two different aspects of the problem require measurement:

- The incidence of cataract responsible for a significant reduction in visual acuity. This represents the greatest impact on society in terms of visual disability, need for health care, and economic and social costs.

- The number of cataracts resulting in irreversible blindness, either from complications of advanced untreated cataracts (e.g. secondary glaucoma) or from complications of surgery. This problem is unlikely to be affected by extensions of health care and constitutes a compelling reason for an expansion of research activities.

A number of methods exist for acquiring this data; however, none of the following is entirely satisfactory:

- *Number of Operations Performed.* Theoretically, this is a reflection of the incidence of cataract and is a practical measure of the totality of the problem. Unfortunately, it depends as much on the availability of surgeons, indications for surgery, and the patient's awareness of the problem as it does on the number and severity of cataracts in the community. For example, the number of cataract extractions in the United States has been estimated at between 300,000 and 400,000 per year.[1] This is an incidence of 175 per 100,000, which is three times the incidence in England.[60] Even so, a survey of one U.S. nursing home revealed that there were many more residents in need of cataract extraction than had actually undergone it.[61] Hence, this method still underestimates the problem to a significant degree and is almost impervious to cross-cultural standardization. It should be clear that the oft quoted figure of 1.4 million new visually disabling cataracts per year worldwide, based on the British operative experience, may be a gross underestimation of the true incidence.[60] Some epidemiologists estimate a minimal figure close to 5 to 10 million for new visually disabling cataracts worldwide.

- *Blindness Registries.* These should provide valid estimates of those blinded by cataract or their sequelae. Unfortunately, scientists are faced with a problem almost unique in ocular pathology: an unknown proportion of those individuals have surgically correctable disease. To be useful, the system must distinguish between these two classes of blindness. Although legally constituted registries have identified twice as many blind people as census methods, they still underestimate the true size of the problem by at least one-third.[62,63] For example, the annual incidence of blindness registration for cataracts in the former Model Reporting Area for Blindness Statistics in the United States was 1.7 per 100,000 population, an estimated 3,400 nationwide.[64] The number that might be expected as a result of surgical complications alone is probably much greater; however, the true complication rate is unknown.

  Published results may not be altogether representative since good results are themselves one of the stongest inducements to publication. But a recent study of 100 consecutive cataract extraction cases performed at a major teaching facility in the United States indicates that only two-thirds of all patients had a final visual acuity of 20/30 or better, whereas in 2 percent, visual acuity was equal or less than 20/200 (W.R. Green, unpublished data, 1975). In most of these cases, poor vision after cataract surgery resulted from preexisting retinal or optic nerve disease.

- *Prevalence Surveys.* Combined with good operative data, prevalence surveys are the most direct means of acquiring the information needed. Theoretically, all cataracts in the population and their sequelae, graded for severity, could be identified. From a practical standpoint, at least in technologically advanced countries, the cost of such studies is enormous and standardization is extremely difficult. The best data available have been generated by the intensive, repeatedly standardized investigation of one limited, relatively

cooperative population in Framingham, Massachusetts. Forty-six percent of those aged 75 to 85 had cataracts which reduced their visual acuity to 20/30 or less.[65]

Priorities and Recommendations

- Search for epidemiologic data. An expansion of carefully conducted epidemiologic investigations into the nature and causes of senile cataracts is needed. Of special interest is the possible association between the occurrence and maturation of senile cataract and diabetes, high plasma phospholipid levels, or ultraviolet light; the confirmation and explanation of the apparent increased incidence of cataracts in the population of the Punjab, India; and the effective interaction of those interested in cataract epidemiology with large, well-organized longitudinal studies of human populations in the United States.

3

Diabetic Cataract

TEN TO FIFTEEN percent of patients admitted for senile cataract surgery in the United States and England have overt diabetes mellitus or abnormalities in their blood sugar levels.[58] Thus, it is possible that diabetes mellitus may contribute to the development of senile cataracts that require surgical removal. Cataracts in patients with diabetic retinopathy add to the visual loss caused by the effects of long-term diabetes mellitus.

Accomplishments

Because of cataract research supported by NEI, the pathogenesis of diabetic cataracts is now well understood. In diabetes, glucose is found in excess in the lens. This leads to glucose conversion into sorbitol,[66] a sugar alcohol that accumulates in the lens and attracts water osmotically.[2] Excessive water damages the lens fibers, and vacuoles appear in the lens cortex. The result is the loss of electrolytes, amino acids, and inositol needed for lens viability.[2]

The conversion of excess glucose to sorbitol in the lens is catalyzed by the enzyme aldose reductase. These diabetic cataracts, however, can be retarded or prevented by lowering blood sugar levels with insulin or by lowering the sorbitol levels in the lens with inhibitors of the enzyme aldose reductase.[2] The features of this enzyme and its regulatory role in sorbitol formation are being investigated in detail. In addition, two groups of NEI-supported investigators are testing drugs and chemicals which inhibit lens aldose reductase in the test tube and in laboratory animals to develop an effective means of delaying sugar cataract. Among these, the bioflavonoids appear extremely promising.[19] Such studies may lead to the development of drugs which can be used either to delay or slow the formation of diabetic cataract in humans.

Testing of aldose reductase inhibitors in diabetic animals also proceeds at an accelerated pace, and different methods for delivering drugs to the lens are being explored. Delivery of bioflavonoids to the lens in the form of eyedrops may provide an effective method of treating experimental diabetic cataracts.

Research Objectives

- Further elucidate the mechanisms underlying the formation of diabetic cataract

- Develop drugs for slowing or blocking the development of diabetic cataract in man
- Determine whether diabetes can hasten the development of senile cataract

Research Needs and Approaches

- Determination of the mechanism of sorbitol formation by the lens
- Control of aldose reductase activity by pharmacological inhibitors
- Characterization of osmotic damage to the lens fibers in the diabetic lens
- Further definition of the transport of glucose and sugars into the normal lens

Priorities and Recommendations

- Study the chemical pathways involved in diabetic cataract. To understand the formation of diabetic cataract more clearly, the pathways for glucose metabolism and sorbitol formation must be further clarified in humans and laboratory animals. Additional studies are needed on the enzyme aldose reductase which plays a pivotal role in diabetic cataract formation.
- Delay diabetic cataract formation with drugs or chemicals. Further testing of drugs which inhibit aldose reductase in vitro and in laboratory animals is needed. The toxicity and rate of penetration into the eye of these compounds must be determined and efforts made to enhance their penetration into the lens. Studies of vehicles, slow release of inhibitors, and potential measures to enhance the effect of the drug must be performed.

Resource Requirements

There will be only one NEI-supported research grant for *Diabetic Cataract* in FY 1977. The Panel recommends adding four new research grants in FY 1978, bringing the total funding for this subprogram to $370,000. See the tables at the end of this report for further details.

4

Congenital, Metabolic, and Genetic Cataracts

IN THE UNITED STATES, the total prevalence of prenatal cataract is 41,000, but not all cases are first diagnosed in childhood. Almost one-third of these patients are legally blind,[60] many from the permanent sensory deprivation which results from the cataract (see *Sensory and Motor Disorders of Vision* Panel report, Chapter 2). Moreover, among the 49,000 newly diagnosed cases of congenital eye disorders (11,000 of whom are admitted to United States hospitals each year), a large proportion have cataract.[60]

The major causes of genetic cataracts are unknown. Thirty percent of congenital cataracts are inherited in an autosomal dominant fashion, i.e. one of the parents also has congenital cataracts. Less than 5 percent are inherited in autosomal recessive (both parents carry the cataract gene) or in sex-linked fashion (the mother may have cataracts).[60]

Accomplishments

Genetic Cataracts

Studies conducted by NEI-supported investigators have uncovered chromosomal defects in patients with congenital cataract and with malformation syndromes which include cataracts. Currently, a number of experimental models of inherited congenital cataracts are being studied in order to obtain information on the transmission of cataract-producing genes.[67,68] Miniature schnauzer dogs, rats, and mice with inherited cataracts are laboratory bred and their cataracts studied by electron microscopy and chemical means. Teams including veterinary ophthalmologists and basic scientists are studying pedigrees of large animals (dogs, timber wolves, Siberian tigers) with congenital cataract.

Virus-Induced Cataracts

Maternal infection by the German measles virus (rubella) during the first trimester of pregnancy can cause congenital cataract in newborn babies. The isolation of rubella virus from human cataract by NIH-supported researchers during the 1964-1965 rubella epidemic in the United States provided direct

evidence of the cataractogenic effects of viruses in humans.[4] In addition to the RNA-containing rubella virus, DNA viruses, such as herpes simplex or chicken pox virus, can induce cataract in humans. Other viruses are suspected of causing cataracts in children and adults, but development of laboratory techniques to isolate small quantities of viruses from human cataracts is required to prove this. Ideally, compulsory mass vaccination programs, already existing in some states, will reduce the incidence of viral infections during pregnancy and thus decrease the incidence of virus-induced cataracts. A marked reduction in the incidence of rubella cataract during the past five years can be traced to successful mass rubella vaccination programs.

Inborn Errors of Metabolism and Cataract

Galactosemia and Galactokinase Deficiency

Certain congenital cataracts are associated with such inborn errors of carbohydrate metabolism as galactosemia and galactokinase deficiency.[69] In such conditions, carbohydrates derived from milk can accumulate in the blood of newborn babies because of a genetically determined enzyme deficiency. The lens, which also lacks the specific enzyme, accumulates products of galactose metabolism, such as galactitol. The latter exerts its deleterious effects on lens hydration by drawing water into the lens. Thus, vacuoles are formed in the lens cortex which may progress to a complete cataract if galactose (milk) is not removed from the diet. Galactosemic babies who are raised on a milk-free diet can develop normally and avoid cataract. Studies in which galactosemia is simulated in laboratory animals continue to provide excellent models for the mode of action of toxic carbohydrates on the lens. The animal lens, which can be exposed to high levels of galactose in test tubes, also provides a model tissue for laboratory studies of galactose toxicity to cells and its prevention by aldose reductase inhibitors.[2,19]

Mannosidosis

Mannosidosis is a rare condition with results from the lack of the enzyme a-mannosidase and results in a syndrome of Hurler-like facies (resembles a mucopolysaccharidosis), hepatosplenomegaly, and cataract.[70] The cataract results from the accumulation of complex mannose-containing glycopeptides in the lens. Following detection of the carrier state in parents, prenatal diagnosis of this lethal disorder can be made by amniocentesis.

Others

Cataracts are present in other rare, inborn metabolic errors such as cholesterolemic xanthomatosis, Fabry's disease, and Wilson's disease.

Other Disorders of Metabolism

Hypoglycemia

Cataract develops as a consequence of decreased energy supply to the lens in a great majority of children with low blood sugar (glucose) levels.[71] Lack of glucose results in decreased hexokinase activity which, in turn, reduces even further the lens's energy supply.[18] This cataract can be partially reversed by early recognition of the hypoglycemic condition and administration of glucose to the affected babies.

Lowe's Syndrome

This is a sex-linked inherited disorder involving impaired amino acid transport by the kidneys which results in mental retardation, dwarfism, massive aminoaciduria, systemic and urinary acidosis, cataract, and congenital glaucoma. In most cases, surgical extraction of the cataract is required.

The mothers of the affected babies appear normal and have no detectable metabolic abnormality. However, small, fine, punctate opacities which do not interfere with vision are detected in the mothers.[72] This, apparently, is a sign of a carrier for the Lowe's syndrome gene.

Hypoparathyroidism

Congenital, idiopathic, or surgical hypoparathyroidism can cause low blood calcium levels and subsequently result in cataract. The lens requires calcium ions to maintain its transport of electrolytes, water, amino acids, and inositol levels. Lowered calcium levels in the blood cause neuromuscular hyperexcitability, convulsions, and cataract in the various hypothyroidism and pseudohypoparathyroidism syndromes. Oral, intramuscular, and intravenous administration of calcium reverses the cataract and other symptions of the hypoparathyroid state.

Research Objectives

- Further document the occurrence of cataract in association with congenital, metabolic, or genetic factors
- Develop means of preventing these types of cataracts or reversing them once they occur

Research Needs and Approaches

- Definition of how genes regulate the differentiation of lens fibers
- Study of the lens epithelium and fiber culture in test tubes
- Development of methods for studying systemic metabolic abnormalities in human congenital or developmental cataracts
- Determination of the effect of calcium on lens transport and metabolism

Priorities and Recommendations

- Study chromosomal characteristics in humans and laboratory animals with cataract
- Determine inborn errors of metabolism that cause cataract, such as galactosemia, galactokinase deficiency, glycoprotein, and/or lipid storage disorders
- Investigate the cataractogenic effects of viruses
- Investigate the effects of calcium ions on the normal lens and in hypoparathyroidism in humans and animals
- Study lens epithelial cells and fibers in tissue culture

Resource Requirements

In FY 1977 the NEI will fund approximately four research grants costing an estimated $263,000 in the subprogram *Congenital, Metabolic, and Genetic Cataracts.* The Panel recommends four more research grants and one new specialized clinical research center grant in FY 1978 at a total cost for funding research in this subprogram of $921,000. The tables at the end of this report list specific recommendations and costs.

5

Cataract Induced by Drugs and Radiation and Occurring Secondary to Other Eye Disorders

CATARACT CAN RESULT from high dosage of certain drugs or from other ocular disorders, and it may aggravate existing visual impairment from these causes.

The lens is susceptible to the effects of drugs used to treat other ocular or systemic conditions. Cataract can develop in patients who are receiving large doses of systemic corticosteroids such as those administered to suppress immune reactions which follow kidney transplantation or to children affected by nephrosis or asthma. Cataract can also result from the prolonged application of corticosteroid eyedrops either to control ocular inflammation (as in uveitis) or to prevent the harmful effects of inflammatory reaction on the anterior segment of the eye.

Experimental studies on animals and on extracted human lenses indicate that near-ultraviolet light may have deleterious effects on lens transparency. This has led to speculation that chronic ultraviolet radiation from either the sun or from artificial sources could contribute to the development of cataract in humans. There is no evidence to support this hypothesis at the present time, but the subject deserves further investigation.

Damage to the lens caused by trauma accounts each year for a major part of the visual impairment in the 198,000 people who suffer open wounds of the eye in the United States.[1] Cataract may result from direct perforation of the eyeball and the lens capsule by sharp tools or foreign bodies.

There are approximately 100,000 Americans suffering from retinitis pigmentosa or allied retinal degenerations (see *Retinal and Choroidal Diseases* Panel report, Chapter 1). Visual impairment in those under age 30 may be further aggravated by cataracts which develop in the posterior part of the lens (posterior subcapsular cataract). Many such people require cataract surgery to preserve the minimal sight remaining to them.

Accomplishments

Drug-Induced Cataracts

NEI-supported studies of the rabbit lens in tissue culture have partially clarified

the effect of steroids on the lens and their role in cataract formation. It appears that steroids increase the permeability of lens cell membranes, thus causing abnormal movement of ions.[46] Cataract also results from topical administration of Phospholine iodide, an anticholinesterase agent used to control high intraocular pressure in glaucoma. Recently, an investigator succeeded in inducing a similar cataract in monkeys.[73] Triparanol, a drug which lowers serum cholesterol, can induce cataract in humans and in rats. Triparanol blocks the synthesis of cholesterol and thereby can cause abnormal chemical composition and defective permeability of the lens membranes which eventually leads to cataract formation.[74] Chlorpromazine, a drug widely used in psychiatric institutions as a central nervous system depressant, produces cataract both in humans and in laboratory animals.[7]

Ultraviolet Light in Cataractogenesis

The concept that ultraviolet light can cause cataractous changes in the lens is based on studies of rodents and observations of chemical alterations in human lenses and in isolated proteins in vitro.[75,76] Mice exposed to light from 320 to 400 nm. (UV-A) in intensity for 12 hours a day for several months up to two years had the following lens changes: cytotoxic effects on epithelial cells leading to abnormal differentiation, accumulation of insoluble proteins and losses of certain soluble proteins, and increased fluorescence and excited-state content. The gross result was anterior cortex opacities after about one year of ultraviolet light exposure. In addition, known sensitizers to ultraviolet light (psoralen, aminotriazole) can cause cataracts in mice, rats, and guinea pigs.

In human lenses exposed to ultraviolet light in vitro, an increase in yellow pigment develops during a period of several days. Homogenized human lenses exposed to sunlight develop a pigment with distinct fluorescent properties Physical and chemical changes induced in the proteins of this material suggest that tryptophan photoproducts were formed (i.e. N-formylkynurenine) in the proteins. Losses of tryptophan and histidine from the proteins were also observed. An investigator has found tryptophan oxidation products in human lenses (glucosides of 3-OH kynurenine and others) which are known to be photosensitizers for near-UV light.

Other substances with fluorescent properties similar to tryptophan oxidation products have been found to be associated with specific peptides in human lens proteins. When exposed to ultraviolet light in the presence of tryptophan, human lenses and their proteins develop an abnormal 360 nm. excited and 440 nm. emitted fluorescence with similar properties to some of the aforementioned substances found in the lens.[75]

Of the tryptophan photoproducts formed by exposure to ultraviolet light, one inhibits growth and differentiation of cells by interfering with chromatin (some evidence that it does this to lens epithelial cells has been obtained), and another binds to proteins so as to alter their physicochemical properties. The latter product has been shown to alter chemically calf lens gamma crystallins, to interfere with the actions of certain enzymes which are important for normal lens metabolism, and to inhibit catalytic action (i.e. catalase of liver, cornea, and lens epithelial cells).

Cataract in Other Eye Disorders

Injuries

Management of traumatic cataract involves suturing open wounds, controlling

ocular inflammation by corticosteroids, and controlling bacterial infection by antibiotics. Promising results have been obtained by adapting surgical instrumentation originally designed for suction and aspiration of the vitreous to the removal of traumatic cataracts.

Inflammation

It has long been known that uveitis can result in a breakdown of the blood-aqueous humor barrier which prevents entrance of blood or substances from the plasma into the eye. It has also been suspected that some factors originating in the blood or plasma may cause cataract in uveitis. Recently, one group of investigators succeeded in identifying lysophosphatidyl choline, a plasma lipid, as the main cataract-inducing agent in uveitis.[20] Attempts are now being made to prevent the cataractogenic effects of this lipid by blocking its site of action. It also appears that lysophospholipids may potentiate the toxic effects of corticosteroids on the lens by opening up the spaces between the lens membranes, thereby making the drug accessible to the lens fibers.

Research Objectives

- Determine the concentrations of drugs administered for treatment of systemic or ocular diseases that cause lens toxicity or cataracts
- Clarify the role of radiation in the formation of cataracts
- Study the role of lysophospholipids in cataract formation secondary to uveitis
- Determine the best methods for managing traumatic cataract

Research Needs and Approaches

- Determination of the mechanism of drug-induced cataracts and cataracts which result from lens injuries
- Investigation of the chemical factors in aqueous humor that contribute to cataract formation
- Investigation of the role of radiation, including ultraviolet light, in cataractogenesis

Proof is still lacking that ultraviolet light can damage intact human lenses. Comparisons are necessary between cataracts in populations where exposure to sunlight is high and others where it is low.

Epidemiologic studies which compare the various levels of light exposure with cataract incidence among nonmigrating populations are needed. Although senile brunescent cataract is the most likely type to be accelerated by exposure to ultraviolet light, an explanation for the presence of high levels of pigmented, highly aggregated proteins, especially in the nucleus, is required because ultraviolet light would affect only the anterior-central portion of the lens. However, pigment formation may occur in the cortex and eventually become incorporated into the nucleus.

Priorities and Recommendations

- Determine the dose/response characteristics of certain drugs which induce cataracts in humans
- Test drugs in laboratory animals or in lens culture prior to administering to humans
- Conduct controlled studies of the ocular effects of ultraviolet light in humans and in laboratory animals
- Determine further the role of phospholipids in cataracts secondary to uveitis, ocular inflammation, and retinitis pigmentosa

Resource Requirements

In FY 1977 there will be approximately four NEI research grants funded in the subprogram *Cataract Induced by Drugs and Radiation and Occurring Secondary to Other Eye Disorders*. Total estimated NEI funding for this subprogram in FY 1977 will be $263,000. The Panel suggests adding five new research grants in FY 1978 raising total NEI funding of this subprogram to $648,000. Specific information is contained in the tables found at the end of this report.

6

Dislocated Lens

THE LENS IS maintained in position by the zonules, its suspensory ligaments. Inherited disorders (Marfan's syndrome), trauma, or homocystinuria (an inborn error of metabolism) account for a significant number of adult patients who suffer visual impairment due to dislocation of the crystalline lens. In addition to reduced visual acuity, the eye with dislocated lens suffers disturbances in size, shape, and color of the retinal images. In children of age six or younger, these visual abnormalities result in irreversible visual damage because of the associated amblyopia. When the lens is dislocated, other damage to the eye can occur, such as secondary glaucoma which results from the dislocation of the lens into either the vitreous cavity or the anterior chamber. The latter occurrence can also lead to corneal edema. In such cases, surgical removal of the lens is indicated.

Accomplishments

During the past ten years, NEI-supported investigators have found two major types of homocystinuria with dislocated lenses. One type may be corrected by administration of pyridoxine (vitamin B_6) where the other may not.[77] Pyridoxine therapy has been found to be of great value in preventing hemorrhagic complications from general anesthesia in treating patients with homocystinuria and dislocated lenses. Further, these findings have opened the door to the possible correction of enzyme deficiencies in inborn errors of metabolism by administration of enzyme cofactors.

In two laboratories, studies of the anatomical structure and chemical composition of the lens zonules in humans and laboratory animals are in progress. These studies have clarified some of the possible genetic or chemical abnormalities which cause dislocated lenses in humans.

Possible abnormalities in structural protein composition are being sought in the inherited Marfan's syndrome and in its many variations of genetic expression. Biochemical abnormalities in patients with sporadic dislocation of the crystalline lens are also being sought by NEI-supported researchers.

The optical effects of a dislocated lens can often be at least partially corrected by an eyeglass or contact lens. In selected cases, the use of modern surgical techniques has made possible the successful removal of dislocated lenses;

however, this is a difficult procedure which poses some risk to vision and to the eye itself.

Research Objectives

- Understand the genetic basis of lens dislocation
- Clarify the chemical and biochemical composition of the zonules
- Evaluate the usefulness of and indications for surgery in preventing physical damage to the eye or amblyopia from dislocated lenses

Research Needs and Approaches

- Determination of the structural protein composition in the inherited Marfan's syndrome and in other genetic disorders causing lens dislocation
- Investigation of the structure and function of the zonules
- Development of surgical methods for correction of dislocated lenses
- Improvement of optical corrections for children with dislocated lenses

Priorities and Recommendations

- Investigate the morphological structure and chemical composition of the zonules
- Identify metabolic abnormalities in genetic disorders associated with dislocated lenses
- Study the effects of dislocated lenses on visual acuity and the prevention of amblyopia in children by early surgery

Resource Requirements

Total NEI funding in FY 1977 of research on the *Dislocated Lens* will be approximately $65,000 to support one project in this subprogram. The Panel recommends adding one more research project and one specialized clinical research center grant in FY 1978. These additions will raise total NEI funding of research in this subprogram to $492,000 in FY 1978. The tables at the end of this report provide additional information.

7

Accommodation and Optical Problems of Cataract and Aphakia

ASIDE FROM THE importance of cataract per se, other problems involving the lens—or its absence—are the cause of varying degrees of visual impairment and thus warrant consideration in this report. In addition, cataracts which are not ready for surgery cause many people great difficulty, particularly when the condition advances more rapidly in one eye than the other.

Accommodation

The refractive power of the lens is approximately 20 diopters. This varies as the lens focuses at distances of more or less than 20 feet. When focusing at near ranges, the lens changes in shape, a process known as accommodation. The dioptic power thus acquired is known as accommodative power and varies with age, being greatest in the infant and child and decreasing progressively with aging. After age 40, the accommodative power of the lens usually begins to decrease to the point that an image cannot be focused on the retina if an object is held at distances less than ten inches from the eye. Thus, reading glasses are needed. This partial loss of accommodative power is known as presbyopia, and a majority of people age 40 or older are affected.[78]

Optical Problems of Patients with Cataract

The swelling of the lens which accompanies early cataractous changes induces myopia (or reduced hyperopia) and causes refractive aniseikonia. In refractive anisometropia (including aniseikonia), a refractive difference of one diopter results in image size differences in the two eyes of from one percent to one and one-half percent.[79] It is generally agreed that a one percent difference in image size is sufficient to cause asthenopic symptoms of aniseikonia in those sensitive to such differences. In the course of cataract development, a process often occurring over many years, lens power increases of three to five diopters are not uncommon. The problem is not appreciated in most instances because both lenses are usually affected as cataract formation advances, and imagery in the more affected eye becomes progressively poorer because of light scattering and other factors. Yet, these image size effects should not be overlooked and may be part of the symptomatic concerns of the patient. These size changes can usually be corrected by simple optical procedures.[80]

Optical Problems of Aphakia and After Cataract Surgery

Aphakia in Children

Absence of the lens in infants and children, resulting from either hereditary or congenital factors or following cataract extraction, presents special problems. If the eye is otherwise normal, there is a critical need to provide a suitable optical correction as soon as possible if permanent visual loss from sensory deprivation is to be prevented.

Aphakia in Adults

The visual problems associated with aphakia are curious in some ways. Cataract surgery is generally welcomed with enthusiasm by the patient. He or she is delivered from a cloudy world and is delighted with being able to see again. However, among groups of patients who have undergone cataract extraction, there are plateaus of relative satisfaction. More sensitive individuals are troubled by the image size differences inherent in eyeglass correction, weight of the glasses, lens aberrations, blind areas in the visual field, and/or field restrictions. Thus, following successful cataract surgery, it is important to select the visual correction that is most acceptable to the individual patient.

The problem is compounded in unilateral aphakia because there are substantial image size differences between the two eyes which have to be overcome. An eyeglass correction results in an approximate 20 to 25 percent difference in image size between the two eyes. These are totally unreconcilable. Contact lens correction results in a 9 percent image size difference. Contrary to much that has appeared in the literature, it appears that many individuals cannot centrally fuse this 9 percent size difference between the images of the two eyes.[79]

Accomplishments

Accommodation

There has been considerable research on measuring the resting point of accommodation.[81-85] At low luminance levels and in nonstimulated visual fields, the eye focus adjusts to a modest accommodative level. The significance of this response has long been debated. Is it a resting point or a neutral point between sympathetic and parasympathetic accommodation? More work is needed to clarify the nature of this response.

The interactions between the lens and the ciliary body, and changes associated with aging which occur in that relationship, are still unclear.[82] Although it is possible to evaluate the curvature of the lens, it is difficult to assess the activity of the stimulated ciliary body. It is possible, however, to measure an electrical potential related to ciliary body activity. Recently, another measure termed "impedance cyclography" has been used as an index of ciliary body contraction.[82,83] In this technique, a current is passed through the ciliary body by creating an alternating voltage between electrodes. Measured impedance seems to be largely dependent upon the amount of blood in the path between the two electrodes. This technique allows an indirect measure of muscle contraction through evaluation of changes in blood volume during initial phases of ciliary body muscle contraction. An attempt has been made to relate changes in

impedance (and/or potential) during ciliary body contraction to parallel measures of lens curvature. Such changes are then considered as a function of age.

Optical Problems of Aphakia and After Cataract Surgery

Aphakia in Children

There is a critical period in the development of one or both eyes during which unimpeded natural image formation is necessary for the proper development of the visual neural system. Thus, in children with congenital cataract, it is important to remove the cataract (or other impediment to fine-image formation) if full visual potential is to be achieved. This should, however, be performed at a time consistent with the safety of the child. Upon removal of the cataract, prompt steps to correct vision should be initiated. The introduction of the soft contact lens has made possible the immediate visual correction of the newborn child. The lens can be handled and sterilized by the child's mother. If the cataract is unilateral, then one must be concerned with image size differences. The surgeon is faced with the problem of selecting the best way of helping the aphakic eye catch up with the normal eye or at least to optimize its performance characteristics. A child with bilateral aphakia must be helped to catch up visually with the child who has not been subject to sensory deprivation amblyopia.

Recently, methods have been developed for using soft contact lenses in the correction of unilateral or bilateral aphakia in children to help them make the best use of their residual visual function.[86,87] However, poor understanding of infant eye development impedes aiding aphakic children achieve full recovery and/or optimal use of residual function.

Thus, if a young child suffers an injury to one eye, and the cataractous lens must be removed, vision may be restored promptly with a suitable contact lens if there is no additional damage to the retina. However, a majority of these patients subsequently develop exotropia because they cannot fuse images from the two eyes due to differences in retinal image size between the aphakic and the normal eye. To prevent exotropia, the aniseikonic size differences between the two eyes must be corrected. There is proof that a contact lens in unilateral aphakia may be inadequate for correction of the residual size difference. By applying a plus overcorrection (about +6 diopters) to the aphakic contact lens and a negative correction in the eyeglass frame, it is possible to reduce the image size in the aphakic eye so that the binocular vision of most patients falls within the range of fusion. This overcorrection of the contact lens and the addition of minus to the eyeglass lens creates an inverted (backwardly aligned) Galilean telescope.[80 86]

Aphakia in Adults

Image size differences between the two eyes can be corrected with an intraocular lens implant in adults.[16,55] This is one of the true advantages of such a device. Thus, it is possible to resolve optically the image size differences in the two eyes, either by external or internal correction, the ultimate aim of which is restoration of something approximating normal binocular vision. Clearly, the action taken in such cases depends upon the patient's status and consideration of both the potential benefits and risks. The great majority of patients receiving an intraocular lens implant for correction of aphakia are 70 years of age or older.

Research Objectives

- Further understand the processes underlying normal accommodation and how they are affected by aging
- Determine the influence of aphakia on the normal visual development of infants and children
- Develop improved methods of restoring vision following cataract surgery to those individuals with dislocated or congenitally absent lenses
- Determine optical problems of patients with cataracts and develop means for their correction

Research Needs and Approaches

Accommodation

The evaluation of the optical properties of the lens, the lens system as a whole, and the mechanism of accommodation has long been of major interest to clinicians and researchers.[78] Yet, in spite of broad experience in this area, surprising gaps still exist in understanding of the processes associated with accommodation. Work has been directed toward a limited set of problems, and broad questions of functional pertinence remain unresolved, some of which have important clinical implications. For example, the nature of the stimulus (or stimuli) which controls accommodation is still not understood. Several different parameters of the ocular image have been implicated, and it seems that a number of these can stimulate accommodation. Yet, virtually all of these studies have overlooked the important fact that the individual can learn to accommodate voluntarily without the presence of any stimulus per se. NEI-supported investigators have shown that young college students can be trained to accommodate routinely about nine diopters in total darkness.[81] Many questions arise from such considerations, e.g. could a combination of voluntary effort and image qualities be implicated in learning the accommodative response?

In recent years, it has been learned that curvature and thickness of the nucleus of the lens can alter with accommodation and that the absolute length of the eye may be modestly changed when marked accommodation takes place.[84] Of particular interest to the clinician is research on how accommodation causes stretching of the retina. In the human retina with marked accommodation, the ora serrata moves forward approximately one-half nm. The stretch of the retina over the noncompressible vitreous sphere increases the total area (not volume) of the retina and induces force which must be transmitted across its entire surface. Two investigators have been able to show that these effects can be observed around the posterior pole of the eye and result in characteristic (and sometimes surprisingly large) alterations in monocular space perception.[85] At the same time, retinal receptor alignment can be shown to be altered transiently by the same process. Implications of this finding are numerous. First, the act of accommodation induces transretinal forces upon the retina. Any analysis of retinal integrity must consider this factor. And second, in considering the question of the effect of aging on the ciliary body, it is important to know whether someone with presbyopia uses the same amount of ciliary body effort when accommodating one or two diopters today as he or she did when younger.[82] If a large change in ciliary

body effort must be induced to obtain modest accommodation, and this effort puts added strain upon the retina, this fact could have clinical significance.

Optical Problems of Aphakia and After Cataract Surgery

There is a paucity of data on the optical properties of the infant eye. Biometric research is needed to determine such factors as the normal development of eye length and of the refractive power of lens and cornea. Otherwise, planning of refractive and size correction in childhood aphakia is subject to significant error.

Priorities and Recommendations

- Investigate the relationships between the ciliary body and the lens, particularly with regard to aging and presbyopia, and their effects upon the retina.
- Study the restoration of more normal vision in aphakia. With contact lenses, many problems associated with aphakic eyeglass correction may be reduced. With intraocular implants and/or inverted telescopes utilizing a contact lens and an eyeglass lens, size differences in the two eyes may be resolved.
- Study how to optimize visual function in children with cataract both before and after surgery in order to reduce the risk of sensory deprivation amblyopia.

Resource Requirements

There will be no NEI grants awarded in the subprogram *Accommodation and Optical Problems of Cataract and Aphakia* in FY 1977. The Panel recommends initiating one research grant in FY 1978. Estimated NEI funding of this subprogram will be $69,000 in that year.

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Project and Resource Tables

Table 1: Cataract
Total Resource Requirements by Mechanism FY 1978
(Dollars in thousands)

	Research Grants		Specialized Clinical Research Centers		Contracts		Core Centers		Research Career Awards		Research Training		Total
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	Amt.
Estimated Support FY 1977	68	$4,465	1	$150	0	$ 0	4	$509	3	$ 73	12	$327	$ 5,524
Additional Requirements FY 1978	37	2,838	2	700	13	1,000	0	106	2	52	6	90	4,786
Estimated Total Support FY 1978	105	$7,303	3	$850	13	$1,000	4	$615	5	$125	18	$417	$10,310

Table 2: Summary of Recommendations by Subprogram

	Estimated Support FY 1977				Additional Requirements FY 1978				Estimated Total Support FY 1978			
	Number of Projects				Number of Projects				Number of Projects			
Subprogram	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)
1. The Normal Lens	38	1	0	$2,646	7	0	0	$ 539	45	1	0	$ 3,185
2. Senile or Degenerative Cataract	20	0	0	1,313	15	0	13	2,155	35	0	13	3,468
3. Diabetic Cataract	1	0	0	65	4	0	0	305	5	0	0	370
4. Congenital, Metabolic, and Genetic Cataracts	4	0	0	263	4	1	0	658	8	1	0	921
5. Cataract Induced by Drugs and Radiation and Occurring Secondary to Other Eye Disorders	4	0	0	263	5	0	0	385	9	0	0	648
6. Dislocated Lens	1	0	0	65	1	1	0	427	2	1	0	492
7. Accommodation and Optical Problems of Cataract and Aphakia	0	0	0	0	1	0	0	69	1	0	0	69
Other*				909				248				1,157
TOTAL: *Cataract*	68	1	0	$5,524	37	2	13	$4,786	105	3	13	$10,310

*Core Centers, Research Career Awards, and Research Training

Note: The three project and resource tables are explained in the introduction to this volume.

Table 3: Recommendations by Subprogram

Chapter 1: The Normal Lens

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Transport, Metabolism, Chemical Composition			
1. Perform additional biochemical studies of regulatory enzyme reactions, protein organization and structure, transport mechanism and membrane chemistry, synthesis of glutathione and peptides, lipid and carbohydrate metabolism of the animal lens and its zonules (F)	1		
2. Determine chemical composition of the normal human lens including carbohydrates, lipids, proteins, and electrolytes (F)	1		
B. Lens Culture			
1. Develop methods for culturing the human lens and lens cells (F, CR)	1		
C. Lens Embryology			
1. Develop and apply new techniques for studying the embryology and morphology of lens fibers and zonules (F)	1		
D. Protein Chemistry			
1. (See Recommendation A. 1 above)	1		
2. Apply new techniques for the study of lens transparency and transmission of light by the lens (F)	1		
E. Molecular Biology			
1. (See Recommendation A. 2 above)	1		
TOTAL: *The Normal Lens*	7	0	0

(Estimated Number of New Principal Investigators Required, FY 1978-80: 7)

Key:
F — Fundamental Research
CR — Clinical Research
CT — Clinical Trial
RD — Resource Development
[ ] — Counted in another subprogram as noted

Chapter 2: Senile or Degenerative Cataract

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Causes and Pathogenesis			
1. Establish a cooperative cataract research group (CR)	*		
2. Develop and apply new biochemical and biophysical techniques to the study of senile lens and senile cataract (F). Focus particular attention on			2
a. Proteins	2		
b. Electrolytes	2		
c. Lipids	3		
d. Carbohydrates	3		
e. Peptides	2		
3. Develop methods for culturing senile cataract (F)	1		
4. Design photographic, television, and other electronic equipment for documenting changes that occur in the senile human lens and in cataract development (CR)			1
B. Treatment			
1. Organize large-scale clinical trials of intraocular lenses (CT)			10
2. Study intraocular lenses in animals (RD)	1		
C. Epidemiology			
1. Expand carefully conducted epidemiological investigations into the nature and causes of senile cataracts (CR)	1		
TOTAL: *Senile or Degenerative Cataract*	15	0	13
(Estimated Number of New Principal Investigators Required, FY 1978-80: 19)			

*To be supported by supplemental funding of existing research grants held by participants.

Chapter 3: Diabetic Cataract

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Causative Mechanisms			
1. Study the chemical pathways involved in diabetic cataract (F)	2		
B. Pharmacologic Control			
1. Delay diabetic cataract formation with drugs or chemicals (CR)	2		
TOTAL: *Diabetic Cataract*	4	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 4)			

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Gene Regulated Differentiation of Lens Fibers			
1. Study chromosomal characteristics in humans and laboratory animals with cataract (CR)		1 project	
B. Systemic Metabolic Abnormalities			
1. Determine inborn errors of metabolism that cause cataract, such as galactosemia, galactokinase deficiency, glycoprotein, and/or lipid storage disorders (CR)		Genetic Center* 1 project	1
C. Virus-Induced Cataracts			
1. Investigate the cataractogenic effects of viruses (F)	1		
D. Calcium Effects			
1. Investigate the effects of calcium ions on the normal lens and in hypoparathyroidism in humans and animals (F)	1		
E. Tissue Culture			
1. Study lens epithelial cells and fibers in tissue culture (F)	2		
TOTAL: *Congenital, Metabolic, and Genetic Cataracts*	4	1 (including 3 projects*)	0

(Estimated Number of New Principal Investigators Required, FY 1978-80: 6)

*For 1 additional project, see table for Chapter 6, *Dislocated Lens*.

Chapter 5: Cataract Induced by Drugs and Radiation and Occurring Secondary to Other Eye Disorders

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Drug-Induced Cataracts			
1. Determine the dose/response characteristics of certain drugs which induce cataracts in humans (CR)	1		
2. Test drugs in laboratory animals or in lens culture prior to administration in humans (CR)	1		
B. Ultraviolet Light in Cataractogenesis			
1. Conduct controlled studies of the ocular effects of ultraviolet light in human and in laboratory animals (CR)	1		
C. Cataracts in Other Eye Disorders			
1. Determine further the role of phospholipids in cataracts secondary to uveitis, ocular inflammation, and retinitis pigmentosa (F)	2		
TOTAL: *Cataracts Induced by Drugs and Radiation and Occurring Secondary to Other Eye Disorders*	5	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 4)			

Chapter 6: Dislocated Lens

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Zonular Structure and Function			
1. Investigate the morphological structure and chemical composition of the zonules (F)	1		
B. Genetics			
1. Identify metabolic abnormalities in genetic disorders associated with dislocated lenses (CR)		[1 project*]	
C. Therapy			
1. Study the effects of dislocated lenses on visual acuity and the prevention of amblyopia in children by early surgery (CR)		1 project Amblyopia Center** 1	
TOTAL: *Dislocated Lens*	1	1 (including 3 projects**)	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 3)			

*Included in the Genetic Center. See table for Chapter 4, *Congenital, Metabolic, and Genetic Cataracts.*
**For two additional projects, see table for Chapter 7, *Accommodation and Optical Problems of Cataract and Aphakia.*

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Accommodation			
1. Investigate the relationships between the ciliary body and lens, particularly with regard to aging and presbyopia, and their effects upon the retina (CR)	1		
B. Optical Problems After Cataract Surgery			
1. Study the restoration of more normal vision in aphakia (CR)		[1 project*]	
2. Study how to optimize visual function in children with cataract both before and after surgery in order to reduce the risk of sensory deprivation amblyopia (CR)		[1 project*]	
TOTAL: *Accommodation and Optical Problems of Cataract and Aphakia*	1	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 3)			

*Included in the Amblyopia Center. See table for Chapter 6, *Dislocated Lens*.

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Glaucoma

Overleaf: *Measurement of intraocular pressure by tonometry.*

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Foreword

THE OPINIONS AND recommendations presented in this report were arrived at by reviewing and analyzing some 3,000 scientific papers on glaucoma published from 1970 to 1976, by surveying glaucoma research currently supported by the National Eye Institute and other agencies, by identifying the problems in glaucoma that still exist despite recent accomplishments, and by comparing what is being done with what needs to be done.

A comprehensive survey of the problems and a review of ongoing research make it clear that the categories utilized in the *Glaucoma* section of the National Advisory Eye Council's 1975 report, *Vision Research Program Planning*, need to be expanded.

Although the first report categorized glaucoma research according to types of glaucoma—an approach that is applicable mainly to classifying investigations concerned with etiology—there are several lines of study that are not readily accommodated within this taxonomy. For example, the effect of pressure on the optic nerve and the resultant destruction of vision is a concern common in almost every type of glaucoma and is of such importance that it warrants a great deal of investigative attention as a principal category of glaucoma research.

Similarly, it is evident that research on many of the factors that influence intraocular pressure, such as formation and outflow of aqueous humor, must be carried out in normal as well as glaucomatous eyes in order to understand the anatomy, physiology, pharmacology, pathology, and toxicology that relate to important differences between normal and diseased eyes. The study of ocular hydrodynamics, which includes the many factors that influence intraocular pressure, tends to apply not just to single types but to many different types of glaucoma. At present, the greatest number of NEI research grants in the *Glaucoma* program support studies of ocular hydrodynamics. A great many publications in scientific journals are concerned with ocular hydrodynamics without limitation to certain types of glaucoma. Hydrodynamics of the eye thus constitutes one of the principal categories of glaucoma research.

Research on glaucoma treatment, either by medical or surgical means, also may yield information that can be applied to several different types of glaucoma. Although it is extremely important to recognize when a specific form of treatment is called for in a certain type of glaucoma, such as iridectomy for acute angle-closure glaucoma, there are some forms of treatment, such as the use of carbonic anhydrase inhibitors to suppress formation of aqueous humor, that can be used with proper clinical judgment in many types of glaucoma. Similarly, filtration surgery is applicable to a number of different types of glaucoma. Currently, only a small portion of research on glaucoma treatment is specifically

directed to the treatment of particular types of this disease. Most efforts to improve treatment have been generally directed at facilitating the outflow or reducing the formation of aqueous humor, either medically or surgically, with the hope that the results could be applied broadly to various forms of glaucoma. Recognizing these facts, it has seemed appropriate to consider research on glaucoma treatment to be one of the distinctive categories of glaucoma research.

The categories into which glaucoma research seems naturally to fall, and according to which the problems, accomplishments, research objectives, needs, and approaches are to be discussed, are:

1. Etiology of Glaucoma
2. Optic Nerve and Vision Changes in Glaucoma
3. Hydrodynamics of the Eye
4. Medical and Surgical Treatment of Glaucoma

Introduction

GLAUCOMA HAS LONG been recognized as a condition in which the intraocular pressure is generally higher than in normal eyes. In association with elevated intraocular pressure, the optic nerve tends to become deformed specifically at the site where it emerges from the eye, and some or all of the fibers of the optic nerve may die. In proportion to the loss of nerve fibers, vision is lost, resulting in complete blindness in the worst instances and characteristic contraction of the visual field in others. In centuries past, only dramatic acute glaucoma with very high pressure, hardness of the eyeball to touch, and rapid complete loss of vision received much clinical attention, but it is now evident that there exists a much larger number of cases of glaucoma which are chronic and characterized by slight elevation of intraocular pressure that is detectable only by tonometry. In such cases, many years may pass before there is significant change in the appearance of the optic nerve or before visual loss begins. There is another large group of cases which has moderately elevated pressure and experiences a dangerous rate of visual loss unless treated adequately.

Gradually, it has become evident that there are many different types of glaucoma, each having different causes for elevation of intraocular pressure. It will become increasingly important to gain understanding of these various causes as a basis for designing specific means of treatment or prevention for each type of glaucoma. It is for this reason that the Panel places much research emphasis on *Etiology of Glaucoma,* the assignment of cause.

We also emphasize *Optic Nerve and Vision Changes in Glaucoma* because it is necessary to learn how and why the optic nerve becomes deformed and nerve fibers die if there is to be improvement in the means of protecting and preserving them. We count on research on *Hydrodynamics of the Eye* to make clear how the circulation of intraocular fluids derived from the blood influences the pressure in normal and abnormal eyes and how fluid exchanges are influenced by factors such as hormones, nerves to the eye, and drugs. Our emphasis on *Medical and Surgical Treatment of Glaucoma* needs no explanation since it is evident that the goal of research on glaucoma is to cure or prevent this condition, and this requires testing methods of treatment which are designed on the basis of new understanding of etiology, the optic nerve, and hydrodynamics.

The main approaches to glaucoma research are discussed in turn in the following sections.

Etiology and Pathogenesis of Pressure Elevation

For nearly all types of glaucoma, there is imperfect knowledge of cause and pathogenesis. For some types (for example, cysts of the ciliary body) the initiating factors are unknown, but the mechanism of pressure elevation is understood. For others (for example, pseudoexfoliation, pigmentary glaucoma, glaucoma secondary to uveitis), neither the initiating abnormality nor the various steps in the pathogenesis are understood.

To answer these types of questions, observations of the naturally occurring disease must constitute a major approach. In some instances new instrumentation may be needed, such as a device for performing quantitative gonioscopy to understand and classify the various primary angle-closure glaucomas. Studies of the naturally occurring disease may include laboratory examination of biopsy material (e.g. trabecular meshwork specimens and aqueous humor samples) by anatomic, biochemical, or physiologic methods. In a very few types of glaucoma it may be profitable to prove that a certain hypothetical mechanism is capable of producing glaucoma in an animal, but study in animal models often is not of great value in understanding the initiating mechanism in human glaucoma.

Clinical research is of great importance because glaucoma is principally a disease of human beings, but there is serious need for more opportunities to correlate clinical findings with the wealth of information that can be obtained by well-planned and executed studies of the eye after death. Patients who have been thoroughly studied and followed for at least a year before death should be made aware that research on their disease can be greatly promoted by special studies on their eyes after they die. The NEI needs to make a strong educational effort to encourage people with eye diseases such as glaucoma to arrange for making their eyes available after death for studies designed to fill important gaps in knowledge.

Studies are needed to clarify the mechanisms in rubeosis, glaucoma secondary to uveitis, hemolytic glaucoma, infantile glaucoma, and many others. In these cases it may be helpful in treating the disease to understand its pathogenesis so that therapy can be aimed at the causative mechanism. In other types of glaucoma (those resulting from rubella and trauma may be examples), understanding the mechanism will be of academic and scientific interest, but this knowledge will contribute little to the management of patients with these types of glaucoma.

Natural History and Therapeutic Trials

Even without understanding the details of its mechanism, the natural course of glaucoma should be studied to identify predictive factors that may determine the course of glaucoma in different individuals and to compare the effectiveness of the various therapeutic approaches presently advocated. Current teachings are based mainly on a reasonable understanding of the natural history of glaucoma, considerable understanding of the normal physiology of the ocular structures involved, and an adequate armamentarium of drugs. In angle-closure glaucoma, there is information on the natural course in patients who have developed glaucoma, but it is not possible to predict which patients with narrow angles will subsequently develop glaucoma. This is due to inadequate knowledge of pathogenic mechanisms and of the value of provocative tests.

In chronic open-angle glaucoma there is an analogous situation. It has long been known that abnormal intraocular pressure does not always lead to visual loss, but it is not possible to discern adequately which patients with elevated pressure are more or less at risk of losing their vision. Natural history studies

designed to determine predictive factors and studies comparing therapeutic regimens are sorely needed, but they must be carefully designed because the disease is chronic and so slow in its development. Such studies may be major undertakings and will require well-coordinated collaborative efforts among several research teams. In the case of open-angle glaucoma a previous effort of this sort gained some valuable information but fell short of its goal, partly because patients were followed for an insufficient length of time.* Much could now be learned by further study of the patients who participated in that study and whose background data are already on record.

For many secondary glaucomas (e.g. that resulting from neovascularization), there are concepts of their natural course, but firm observations are lacking. Wherever feasible from an ethical standpoint, trials of therapy should include a matched group of individuals who are concurrently allowed to run their natural course or who are given a different treatment.

Also among the studies that might be profitable is an epidemiologic investigation of visual loss from glaucoma to determine which types of glaucoma are most responsible for visual loss and the relative prevalence of glaucomatous visual loss due to late diagnosis, to inadequate patient compliance in the use of prescribed therapy, to inadequate medical practice in the use of available therapy, or to unavailability of adequate means to control specific cases. Common occurrence of the last would underscore the need for more research, and of the first, the need for improved detection and management of glaucoma with available means. Such a study also could lead to improved use of available therapy.

Clinical Examination Methods

New instrumentation may be helpful in caring for patients with glaucoma and in providing improved methods for studying the disease. It might be profitable to support the development of techniques for anterior segment and angle biometry, for quantitative evaluation, topography and physiology of the optic disc, and for automated visual field evaluation, although satisfactory achievement of each of these would be exceedingly difficult.

The clinical study of aqueous humor dynamics has produced pilot information but has not yet proved to be highly practical, in part at least, because the mathematical and conceptual complexity of presently available methods has apparently discouraged many clinicians from confirming and extending the evaluation of the parameters which describe the flow of aqueous humor into and out of the eye. Such difficulties also seem to have discouraged systematic search for new antiglaucoma drugs based on alterations of pseudofacility. There is potential here if more laboratories can be persuaded to undertake studies of these kinds on normal volunteers and on patients with glaucoma. Continued work should be encouraged by appropriate financial support.

Certain recently developed tonometers have advantages for special purposes, but it does not seem profitable to put much further effort in this direction, except for devising an accurate noninvasive method for continuous measurement of intraocular pressure over hours and days and for devising an instrument particularly suited to home self-tonometry.

Home tonometry, in which a relative or friend of the patient is taught to perform this procedure, is potentially a very valuable means to aid in diagnosis, study of low tension glaucoma, characterization of circadian variation in

* Armaly MF: Final report to the National Eye Institute on *Biostatistical Analysis of the Collaborative Glaucoma Study*, Contract Number NIH-NEI-74-2167, May 1977.

intraocular pressure, and evaluation of responses to medications. This procedure should be much more widely used. Schiotz tonometry is usually employed satisfactorily for this purpose; however, development of a simple tonometer which the patient himself could use safely would greatly enhance the likelihood of obtaining additional important data and should be encouraged.

Importance

Glaucoma is a common and serious eye disease. One or two of every hundred adults have intraocular pressures sufficiently above normal to require periodic reexamination to watch for increasing pressure or signs of damage to the optic nerve that may require medical or surgical treatment. Each year, approximately 178,000* new cases of glaucoma are diagnosed, either as a result of routine eye testing that has detected excessive intraocular pressure and associated abnormality of the optic nerve or because of loss of vision previously noted by the patient that is found upon examination to be due to glaucoma.

Glaucoma affects the vision of more than a million people in the United States. It has severely impaired the vision of 207,000 of these people, and it has caused 56,000 to become legally blind. Women have been affected more often than men.

Each year nearly 2 million visits are made to ophthalmologists or hospital eye clinics for diagnosis and care of glaucoma. For 1974, this was equivalent to one of every 16 visits for diseases of vision, eye injuries, or other medical eye care. Eye surgery for glaucoma represents about 3 percent of all eye surgery, and the cost for one year has been estimated to be $8,758,000. However, a large majority of patients who have glaucoma are treated by means of eyedrops and other medications rather than by surgery. In the United States, the total patient cost for one year for one type of eyedrop used in glaucoma treatment is $29 million.

Thus, besides being a widespread and often serious eye disease, glaucoma is an expensive one. Furthermore, if the cost of the time spent by patients in going for necessary measurements of intraocular pressure, measurements of visual field, and other examinations essential to guiding the treatment of their disease were added to the cost to society for aid to those who have lost vision from glaucoma, the sum would be enormous and far out of proportion to the current cost of research aimed at prevention or better treatment of the disease.

Statistics concerning glaucoma have commonly been compiled as though glaucoma were a single disease or, as in hospitalization records, resolved only into general categories such as "primary acute," representing about 40 percent of hospitalizations for glaucoma, and "primary chronic," representing about 25 percent. Actually, there are 30 to 40 known different types of glaucoma which such statistics have lumped together. Some types of glaucoma are very common, and others are very rare. Some of the relatively rare types are the most difficult to treat and most likely to cause severe loss of vision.

The importance of research on particular types of glaucoma relates not only to the frequency of their occurrence but also the incidence of the visual impairment and other symptoms they cause. Many secondary glaucomas, for example, those due to uveitis, neovascularization, and trauma, are less common but are so unresponsive to present therapeutic methods that they frequently lead to serious visual impairment. Some types that are rare (such as congenital glaucoma and glaucoma accompanying aniridia) are sometimes uncontrollable. These warrant

*Except where specifically referenced, incidence, prevalence, and cost statistics quoted in this report can be found in or have been derived from: Westat, Inc, *Summary and Critique of Available Data on the Prevalence and Economic and Social Costs of Visual Disorders and Disabilities*, Rockville, Maryland, 16 February 1976.

proportionately more research effort than do other types, such as the postoperative "enzyme glaucoma," which is common but almost never leads to visual impairment.

Accomplishments

Medical and surgical treatments for glaucoma have been repeatedly improved as a result of laboratory and clinical research. Advances that have been made in distinguishing different types of glaucoma from one another have brought fundamental clinical advances in selecting the best treatments. The causes of several types of glaucoma have been explained, leading to still better treatment. Excellent instruments for measuring and detecting abnormal intraocular pressure have been devised. Inspired by the research of a small number of pioneer investigators and supported mainly by federal grants for research and training, there is a large and diverse group of people who have dedicated their careers to better understanding of glaucoma and its treatments. Specific accomplishments in this field are described under the appropriate subprogram headings.

Goals of Glaucoma Research

- Improve detection and diagnosis of glaucoma to identify patients needing treatment
- Discover the causes of the various forms of glaucoma and how they destroy vision
- Find out how to cure or control the various types of glaucoma and prevent loss of vision
- Rapidly relate the results of experimental and clinical investigation to the management of clinical problems

Summary of Recommendations

THE FOLLOWING ARE highlights of the recommendations chosen by the *Glaucoma* Panel to represent the most important areas of need and opportunity in glaucoma research. A complete list of recommendations for each *Glaucoma* subprogram may be found in the following chapters.

1. Establish the relationship of genetic markers of cells in the aqueous outflow system and of an individual's leukocytes to the development of various types of glaucoma.
2. Determine whether glaucoma affects Blacks or other racial and ethnic groups more frequently, earlier in life, and/or more severely.
3. Improve methods for diagnostic prediction of angle-closure glaucoma and learn why people differ in their response to medical and surgical treatment for angle-closure glaucoma.
4. Elucidate the manner in which the vitreous body is involved in angle-closure glaucoma and its complications.
5. Determine to what degree prostaglandins are involved in glaucoma secondary to inflammation and injury in human eyes.
6. Clarify how aqueous outflow is obstructed in secondary glaucoma, particularly that attributable to uveitis, in order to provide better treatment.
7. Clarify the basic mechanism of glaucoma associated with the exfoliation syndrome, with the aim of better treatment and possibly prevention of the glaucoma.
8. Develop an animal model for neovascular glaucoma in man and conduct experimental research on the stimuli and fundamental mechanisms involved in neovascularization.
9. Develop a primate animal model of chronic glaucoma for life-long investigation and stereophotographic documentation of changes induced in the appearance of the optic nerve head. Make subsequent correlations with histopathology, and with a sufficient number of animals, explore how much variation there may be in susceptibility to injury by a given pressure among different individuals.

10. Evaluate through prospective, controlled clinical research the risk to vision from treatment of systemic hypertension in patients with glaucoma.

11. Establish factors or tests that may indicate varying susceptibility of different types of optic nerve heads to change in cupping and visual fields under the influence of chronically elevated intraocular pressure. Such factors may have predictive value and could serve as a guide to the amount of treatment needed in individual cases. Also, determine whether there is significant relationship of these factors to genetic markers.

12. Clarify the pathogenesis of low tension glaucoma by evaluating the influence of reducing the intraocular pressure, particularly to very low levels, by surgery in one eye to ascertain if this arrests the progress.

13. Ascertain the relative influences of physical factors and of metabolic processes in controlling aqueous humor outflow as well as the manner in which catecholamines and cyclic AMP act, since these are vitally related to the several types of glaucoma. This may lead to improved treatment and possibly even to prevention of some forms of glaucoma.

14. Develop better noninvasive means for measuring and monitoring the rate of aqueous humor formation in patients and in monkeys, because this would facilitate several important lines of clinical glaucoma research.

15. Obtain a complete understanding of the mechanism by which carbonic anhydrase inhibitors influence aqueous formation, and explain why these drugs fail to reduce aqueous formation when topically administered.

16. Find new drugs that increase the rate of aqueous formation for potential application in the treatment of excessive hypotony, such as that associated with choroidal detachment.

17. Increase understanding of how metabolic factors in the tissues that lie between the anterior chamber and Schlemm's canal may be altered in disease, how outflow regulation may be affected by hormones and drugs, and how these tissues may be involved in turnover of mucopolysaccharides that may be important in governing resistance to aqueous outflow.

18. Establish the clinical functional significance of uveo-scleral relationships, and particularly explain how detachment of the choroid and ciliary body may reduce formation of aqueous humor, with the aim of potentially applying this knowledge to the development of new forms of treatment of both hypotony and glaucoma and also to the development of a good animal model.

19. Establish whether the intraocular pressure variation results from variation in aqueous formation or in resistance to outflow, and establish more exactly whether this is in response to hormonal, neural, hypothalamic, or other influences, with the ultimate goal of applying this knowledge to the development of better means of regulating the pressure.

20. Devise a noninvasive device for continuously monitoring intraocular pressure in patients for many types of clinical glaucoma research.

21. Determine in which types of eyes subject to angle-closure glaucoma that treatment with miotic eyedrops acts favorably, causing opening and widening of the angle, and in which types of eyes the same miotic eyedrops act unfavorably, aggravating the shallowing of the anterior chamber and causing the angle to close, with the ultimate aim of understanding these differences and for differentiating these types of eyes prior to choosing treatment.

22. Appraise the value of laser coagulation of new-formed vessels in the anterior chamber in the treatment and prevention of neovascular glaucoma and the value of photocoagulation of the fundus in the treatment and prevention of neovascular glaucoma in cases of diabetic retinopathy and of occlusion of central retinal vessels.

23. Improve the results of filtration surgery in children and young people, and also in certain older people who have an extraordinary tendency to scar down their blebs, by a combination of experimental and clinical research.

24. Clarify the basis for cataract formation after glaucoma operations, with the aim of developing means to reduce the incidence of this common and important complication.

1

Etiology of Glaucoma

ALTHOUGH THERE ARE probably as many different causes of glaucoma as there are types, for the purpose of considering research opportunities in the etiology of glaucoma it is convenient to divide this subprogram into four main categories: Developmental Glaucoma, Primary Open-Angle Glaucoma, Primary Angle-Closure Glaucoma, and Secondary Glaucomas. Under each, the *Glaucoma* Panel discusses recent accomplishments, current research objectives, and major research needs and opportunities. Recommendations for areas of emphasis and projections of estimated resources that will be required to carry these out conclude each section.

Developmental Glaucoma

Fortunately, the developmental anomalies of the eye that cause glaucoma are rare, but they are a public health problem because they may lead to severe and permanent loss of vision at an early age. Though a majority of patients benefit dramatically from suitable surgery in infancy, those that do not respond to early surgery present severe management problems, often requiring repeated hospitalizations and repeated surgical procedures under general anesthesia.[1–3]

Several specific types of developmental glaucoma are recognizable. Early differential diagnosis is most important to choosing proper treatment and to determining whether existing treatments may be effective. Although it is unrealistic to conceive of eliminating developmental glaucomas, research on improved clinical management should make it possible to reduce the incidence and degree of visual loss they cause.

Accomplishments

Progress against congenital aniridia glaucoma is a good example of recent accomplishments in study of developmental glaucoma. Babies who are born lacking most of their irises are said to have congenital aniridia; they tend to develop severe glaucoma during childhood and adolescence. Clinical studies supported by the National Eye Institute have provided an explanation for the gradual development of this glaucoma based on a discovery that the fragment of iris that is present at birth can gradually move forward over the trabecular

meshwork in the angle of the anterior chamber. In this position, it may obstruct the drainage of aqueous humor from the eye, causing the pressure to rise.[4] In the early stages of this type of glaucoma, treatment with standard antiglaucoma eyedrops, such as pilocarpine, is effective in reducing the intraocular pressure. Later, additional treatment with oral carbonic anhydrase inhibitor drugs is helpful, but when this form of glaucoma becomes too severe for medical management, it also becomes extremely difficult to control by surgery. The recognition of the mechanism responsible for the development of congenital aniridia glaucoma has pointed the way to possible prophylactic procedures. Surgical separation of the iris fragment from the angle wall is now being evaluated to determine whether it may reduce the incidence or severity of this kind of glaucoma.

Research Objectives

- Find ways of preventing or ameliorating the effects of congenital glaucoma
- Develop improved means of treating developmental glaucoma by medical and/or surgical means

Research Needs and Approaches

Many clinical features of the developmental glaucomas remain to be described, and proposed management programs require testing. Genetic and environmental factors that may play a role in the pathogenesis of these disorders should be sought. Opportunities exist for research to determine the efficacy of newer antiglaucoma operations, such as trabeculotomy ab externo and laser trabeculotomy.[5-7] There are also opportunities for testing the efficacy of new drugs or drug delivery systems, as well as for developing anesthetic or tranquilizing agents that do not alter the intraocular pressure when the infant has to be examined and evaluated under general anesthesia. There is also need and opportunity for developing means of objectively assessing the status of the infant visual system.

Some patients who undergo surgery for congenital cataract develop a type of postoperative glaucoma which may be very difficult to control.[8,9] A systematized study of children with congenital cataract is needed to detect any tendency to glaucoma before the operation. These children should be studied systematically again after surgery to learn more about how this form of glaucoma is induced. Such studies could be performed readily with presently available methods, and the knowledge gained would very likely lead to earlier diagnosis and to modification in operative technique that might reduce the incidence of this kind of glaucoma.

Although it is highly improbable that even enormous expenditures of effort will eliminate developmental glaucomas, it is reasonable to expect that research designed to gain an understanding of the cause of these diseases can reduce their medical and societal impact.

Research on the rarer forms of glaucoma, particularly the developmental types, may be facilitated and made most economical and effective by developing a small number of clinical centers which could attract a sufficient number of patients with these conditions for adequate study. Alternatively, cooperative multicenter programs could be developed in which a uniform research protocol is used for study of a smaller number of rare cases. Resultant information could be centrally assembled and analyzed and disseminated nationwide. Similarly, a national

registry for histologic surgical or postmortem specimens could help in the study of the rare developmental glaucomas.

Priority and Recommendation

- Elucidate in aniridia the reasons for the changes that take place in the angle as glaucoma develops and evaluate the role of prophylactic surgery

Resource Requirements

The fiscal year 1977 funding for investigations in the etiology of Developmental Glaucoma will be approximately $200,000 to support three research grants. For FY 1978 the Panel recommends three additional research grants. The estimated FY 1978 total funding for this area of research will be $437,000. See the tables at the end of this report for more details.

Primary Open-Angle Glaucoma

Primary open-angle glaucoma is the most common of the glaucomas and is the cause of much of the loss of vision associated with this disease. In this form of glaucoma, intraocular pressure may become gradually and progressively elevated without symptoms and may significantly reduce the field of vision in one or both eyes before it is noticed by the affected individual.

Accomplishments

When primary open-angle glaucoma is diagnosed early—at the very onset of damage to the optic nerve—it usually can be adequately controlled during the patient's lifetime by medical and surgical treatment.[2,10,11] Only in a small proportion of cases in which diagnosis has been made early does severe loss of vision occur in spite of all therapeutic efforts. In general, the more advanced the disease at the time of diagnosis, the poorer the prospect of retaining vision. Improved means of both early detection and treatment are needed.

In recent years, research on the genetic aspects of the etiology of primary open-angle glaucoma has been of particular interest because many patients have a definite family history of the disease. Furthermore, tests of large numbers of people have established that application of corticosteroid eyedrops causes a rise of intraocular pressure more commonly in patients who have this type of glaucoma, and in relatives of these patients, than in unrelated individuals.[12-18] Although recent testing has revealed unexpected variability in this response to steroid drops in repeated testings on the same individuals, and unexpected differences in the response of identical twins, important work has continued in relation to the original observations.[19-21]

Plasma cortisol has been shown to be suppressed by an oral dose of corticosteroid more readily in patients with primary open-angle glaucoma than in nonglaucomatous patients. Leukocytes from blood samples of patients with primary open-angle glaucoma have been found to respond differently to corticosteroids than those from people without the disease. These tests should

help in determining to what degree primary open-angle glaucoma may be related to certain other glaucomas which appear clinically similar in some aspects and dissimilar in others.[22,23]

Research Objective

- Determine the underlying cause(s) of primary open-angle glaucoma

Research Needs and Approaches

Several practical improvements have been made in controlling open-angle glaucoma, but none can be considered a cure of the underlying disease. Current treatment generally consists of means of reducing intraocular pressure by facilitating outflow or suppressing formation of aqueous humor and has not been specifically developed from knowledge of the pathogenesis of the disease.

Scientifically, it is attractive to think that if the most fundamental details of what causes obstruction of aqueous humor outflow in primary open-angle glaucoma were understood, it would be reasonable to hope for development of more specific and effective modes of treatment and, ultimately, for means of cure or prevention.

Research on primary open-angle glaucoma is handicapped, however, because this disease occurs exclusively in human beings—it is not even found in monkeys—and must therefore be investigated principally in human eyes. Types of glaucoma do occur in some animals, and the disease can be artificially induced in animals, but these glaucomas differ in various respects from human primary open-angle disease. One of the most important variations among species is in the anatomy of the aqueous humor outflow system.

While investigations on animal models continue, more research is needed to demonstrate at biochemical and cellular levels differences between patients who have glaucoma and normal individuals, including studies of lymphocyte transformation and other cellular mechanisms and immunologic studies of human leukocyte antigen (HLA) types.[20-24] It may also be fruitful to look for genetic markers relating to primary open-angle glaucoma in cells other than leukocytes, especially those of the aqueous outflow system.

Some ophthalmologists and biostatisticians have an impression that Black men in the United States may be prone to develop open-angle glaucoma at an earlier age and with more serious damage to the optic nerve and vision than generally occurs among the White population.[25,26] Because of the severe economic consequences of blinding disease among young wage earners, it is essential that this potentially important clinical impression be systematically studied by comparing populations of Black and White people of similar age distribution. In designing such a study, consideration must be given to the influence of geographic and tribal or racial origins of the individuals studied to determine whether, in fact, Black males are more prone to early development of severe open-angle glaucoma than Whites, and whether those of a particular origin are especially susceptible. For this purpose, it would seem that extensive testing and correlation of HLA types might serve as a basis for subdivision and study of the population in appropriate categories.

Preliminary studies of this type have been started, but they will need to include larger numbers of individuals.[24,27] Results suggest so far that it will be important to seek genetic correlations not only with abnormal intraocular pressure and corticosteroid responsiveness but also with differences in susceptibility to optic

nerve and vision changes.[20] It will also be important to ascertain whether sickle cell trait and related hemoglobinopathies are factors that influence the susceptibility of the optic nerve to damage. If the results of these preliminary studies reveal sufficiently important correlations between HLA types and various features of open-angle glaucoma, this will encourage extension of this type of investigation to other racial groups and other forms of glaucoma.

Priorities and Recommendations

- Establish more precisely the relationship of genetic markers in aqueous outflow system cells and in lymphocytes to individual differences in the development of various types of glaucoma
- Determine whether glaucoma affects Blacks or other racial and ethnic groups more frequently, earlier in life, and/or more severely
- Identify genetic markers for primary open-angle glaucoma

Resource Requirements

In FY 1977 there will be approximately ten research grants with an estimated total funding for research in this area of $664,000. The Panel recommends an additional four research grants bringing the total FY 1978 funding of research in the etiology of Primary Open-Angle Glaucoma to $980,000. See the tables at the end of this report for more details.

Primary Angle-Closure Glaucoma

Primary angle-closure glaucoma* is a very important form of glaucoma, ranking only after open-angle glaucoma in prevalence but differing in cause, diagnosis, and treatment. Angle-closure glaucoma can develop and cause blindness with extraordinary rapidity. If the condition is not detected soon enough, some patients become blind in both eyes, though more commonly one eye of a patient is affected first and the vision of the other eye is saved by timely treatment.

Angle-closure glaucoma is caused by contact of the iris with the filtration area of the trabecular meshwork in the angle of the anterior chamber, causing obstruction of the normal drainage of aqueous humor from the eye. It is generally related to anatomical peculiarities of the eye: an abnormally shallow anterior chamber and narrow space between iris and trabecular meshwork in the angle.[28-31]

In some cases, angle-closure glaucoma develops subacutely and causes blurred vision, perception of halos around lights, and aching that leads the sufferer to seek medical attention before serious damage is done to vision. These are the fortunate cases.

*Angle-closure glaucoma has also been known as closed-angle glaucoma, but a survey of 1,000 of the most recent publications on glaucoma shows that the term angle-closure is used five times more frequently.

Accomplishments

Impressive progress has been made in recognizing the causes of angle-closure glaucoma and in diagnosing and treating it, but more eyes would be saved if the diagnosis could be made earlier. The clinical goal in this kind of glaucoma is not only early treatment, but prevention.

Research Objectives

- Develop means of identifying which of those individuals with an anatomic predisposition to angle-closure glaucoma are at greatest risk of an actual attack and loss of vision
- Understand better how angle-closure glaucoma may be precipitated by miotic drops and other factors
- Learn more about the complications of surgery for angle-closure glaucoma and how they may be prevented or treated

Research Needs and Approaches

In a large majority of cases the diagnosis of angle-closure glaucoma is made only after at least one of a patient's eyes has suffered an actual attack, either subacute or acute. Yet, there are reasons for thinking that it should be possible to predict when this kind of glaucoma is imminent and thereby prevent it.

One problem peculiar to angle-closure glaucoma is that simply measuring the pressure in the eye does not provide a warning of an impending acute attack. Even immediately before an attack, the pressure may be entirely normal.

If the patient seeks medical attention after angle-closure glaucoma already has developed, a proper diagnosis can be made by direct observation of the closed-angle with gonioscopy equipment. Eyes that may be predisposed to primary angle-closure glaucoma have an unusually narrow space between the iris and the openings of the aqueous outflow system in the trabecular meshwork, and these eyes tend to have a recognizably shallow anterior chamber between the cornea, iris, and crystalline lens.[2,20,28] However, many eyes that appear to have these same anatomical peculiarities never develop glaucoma. The clinical problem is to identify eyes that are so likely to develop glaucoma that preventive treatment is warranted. Pupillary block has been recognized as a prime pathogenic factor for several decades.[32-35] Eyes with normal anatomic configuration can develop angle-closure glaucoma if something pushes the lens forward against the back of the pupillary portion of the iris.[36-42]

There is need to improve diagnostic procedures, such as by correlating physical anatomic measurements with the development of angle-closure glaucoma, to define within narrower limits those patients at high risk.[29-31]

It would be desirable to have a clinical method to measure the degree of pupillary block, but no good suggestion has been made concerning how to do this.

Provocative tests such as the so-called darkroom, prone position, and mydriasis tests deserve more extensive or continued systematic evaluation for their predictive value.[43,44] Possibly this can best be carried out by means of a cooperative study at several large centers with sufficient numbers of patients, employing a standard protocol and appropriate controls. The results of such a study could provide a standard against which to compare new predictive tests which may be developed in the future.

Apart from predictive or diagnostic tests, there are several other aspects of the etiology of angle-closure glaucoma that merit more investigation. These include studies of the influence of ciliary muscle activity, particularly in relation to the effects of miotic eyedrops on the shape of the anterior chamber.[45] It is a clinically interesting and important enigma that in most eyes with abnormally narrow angles, the application of miotic eyedrops causes the angles to become wider and safer, but in a smaller number of eyes that may appear the same, miotic eyedrops occasionally cause the angle to close and precipitate angle-closure glaucoma.[46–52] A better understanding of the reasons for these important differences in response to miotics would be of great help in selecting the treatment most suitable for an individual case. To start with, an investigation is needed in which the influence of miotic eyedrops on the axial depth of the anterior chamber is measured in a large series of patients and compared with the influence of the drug on the angle.

In some cases an attack of angle-closure glaucoma is completely reversible: under appropriate treatment the angle opens completely, and the outflow system for aqueous humor is restored to normal. In other cases, after an attack of angle-closure glaucoma, some areas of adhesion between the iris and the trabecular meshwork continue to obstruct outflow of aqueous humor. This may involve only a small area and be of little practical consequence, but other cases may involve most or all of the circumference of the angle of the anterior chamber and cause significant or even severe chronic, synechial angle-closure glaucoma. Little has been done to establish what governs the rapidity and extent of development of peripheral anterior synechias during attacks of angle-closure glaucoma though better understanding might suggest means of reducing their tendency to form. Also, little is known about whether some degree of aqueous outflow could be restored by treatment to lyse or separate these synechias, a procedure which is clinically feasible. Additional research in the clinic and on monkeys could help elucidate some of these factors. Specifically, it would help to know whether it is possible to restore function by early lysis of peripheral anterior synechias. If synechias become more difficult to reverse as they age, it would be helpful to know why. All these questions concerning peripheral anterior synechias could be answered through a combination of presently available methods of clinical, experimental, and histological investigation.

Further research is needed to determine whether the aqueous outflow system can be damaged by repeated attacks of angle-closure glaucoma even without the formation of synechias. If this does occur, it is important to determine whether this is a stationary condition or has a tendency to progress as in primary open-angle glaucoma.

There is a rare complication of surgery for angle-closure glaucoma in which the anterior chamber becomes flat and the intraocular pressure becomes high but does not respond to the various medications and operations that are customarily employed in treating this disease.[53,54] This complication has been known as "malignant glaucoma" for more than a century.[55] It earned the epithet "malignant" because it so rarely responded to treatment and so commonly led to blindness, but in recent years far more effective treatments have been devised. Now, in about half the cases, this glaucoma is relieved by combined treatment with cycloplegics, carbonic anhydrase inhibitors, and osmotic agents. In other cases it has been successfully treated by surgical aspiration of the vitreous via the pars plana of the ciliary body and injection of saline and air into the anterior chamber.[54,56]

Though this previously devastating form of angle-closure glaucoma is rare and can now be treated successfully in almost all cases, it deserves more systematic investigation to determine its cause, for it seems to involve fundamental mechanisms that may underlie other forms of angle-closure glaucoma and the

effect of miotic eyedrops in shallowing the anterior chamber.[45-52] There is a likely relationship between the mechanism of shallowing of the anterior chamber and the provocation of angle-closure glaucoma by pan-retinal photocoagulation,[39] and in rare cases, by occlusion of the central retinal vessels.[36-38] These mechanisms have broad clinical implications that are inadequately understood at present.

A widely accepted hypothesis is that malignant glaucoma occurs when an abnormally large proportion of aqueous humor is diverted into the vitreous humor away from its ordinary route through the posterior to anterior chamber.[53] How or why it may be diverted is unexplained, although adhesions of anterior vitreous to ciliary processes have occasionally been observed. It is supposed that the diverted aqueous humor does not pass freely out of the vitreous and thus increases the volume of this body so that it presses lens, ciliary processes, and iris forward to close the angle and cause glaucoma with a flattened anterior chamber. Because this condition is not due to pupillary block, iridectomy does not relieve it, and neither filtration operations nor cyclodialysis is effective.

There is great need to substantiate this hypothesis, particularly to clarify the roles of the aqueous humor and the vitreous humor. A recent proposal to change the name of the condition to "ciliary block" glaucoma, to help distinguish it from "pupillary block" glaucoma, also calls attention to a need for research to clarify the role of the ciliary body.[57]

Another question is whether malignant glaucoma, which has long been considered to develop only as a complication of surgery, can in rare instances also occur preoperatively.[50,51,58] The postoperative complication is precipitated or aggravated by miotic eyedrops which cause the ciliary muscle to contract and the zonules of the lens to relax.[54] It is well known that administering miotic drops to some people who are prone to develop angle-closure glaucoma can shallow their anterior chamber and induce an acute attack, though they have had no surgery.[47-49] A very practical question, therefore, is whether patients whose angle-closure glaucoma is precipitated or aggravated by miotic eyedrops preoperatively should or should not have surgical iridectomy, and if they do undergo surgery, whether they have a significant tendency to develop postoperative malignant glaucoma. This could be answered by a clinical investigation in which both the reaction to miotics and the consequences of iridectomy are examined in a sufficient number of patients over an adequate period of time. It must be learned if malignant glaucoma represents an extreme combination of circumstances that may occur in ordinary cases of angle-closure glaucoma.

Priorities and Recommendations

- Improve methods for diagnostic prediction of angle-closure glaucoma and clarify the differences among patients in their responses to medical and surgical treatment for this disease
- Determine the manner in which the vitreous body is involved in angle-closure glaucoma and its complications

There is also a great need to understand the factors related to angle-closure glaucoma that are discussed in Chapter 3 of this report, *Hydrodynamics of the Eye*.

Resource Requirements

Estimated FY 1977 NEI funding for research in the etiology of Primary Angle-Closure Glaucoma will amount to $200,000 in support of approximately three research grants. The Panel recommends an additional seven research grants in FY 1978 at an increase in funding of $553,000. This will bring the total for this area of research to approximately $753,000 for that year. Further details are contained in the tables at the end of this report.

Secondary Glaucomas

The secondary glaucomas are a heterogeneous group in which elevation of intraocular pressure is produced by some recognizable preexisting condition such as inflammation, degenerative changes, trauma, or neoplasm. The secondary glaucomas are not the most common types of glaucoma, but certain of them are among the most difficult to treat and produce a disproportionately high incidence of blindness. In particular, glaucoma secondary to uveitis is among the most difficult to treat and most damaging of all forms of glaucoma.[2,67-70] Despite the numerous clinical reports that have been published which describe this condition, there is remarkable ignorance of the mechanisms causing uveitis itself.

For each type of secondary glaucoma, there is a need to gain better understanding of the underlying disease process and the mechanism by which it raises the intraocular pressure. This, it is hoped, will lead to development of specific forms of treatment for each condition. However, it seems likely that this approach will require a long time and a great deal of effort. In the meantime, because a great many people are losing their vision and in some cases suffering great pain, there is an immediate need to devise less ideal, temporizing treatments to reduce intraocular pressure without curing the underlying disease. In fact, treatment of the secondary glaucomas is at present based largely on nonspecific general methods of reducing intraocular pressure, e.g. oral carbonic anhydrase inhibitors and epinephrine eyedrops. For glaucoma secondary to inflammation of the eye, nonspecific, anti-inflammatory drugs are used; in the case of visible degenerative conditions without inflammation, miotic eyedrops are administered. When available medical means fail, surgery is employed to improve drainage of aqueous humor from the eye.

These various treatments are certainly of great value, but they are often inadequate for maintaining sufficient reduction of intraocular pressure to preserve vision. This demonstrates the need either for understanding the cause and treatment of the underlying disease or for the development of still more effective nonspecific methods of lowering pressure. In glaucoma secondary to uveitis, both the underlying disease and the glaucoma are in some cases destructive to the eye.

Accomplishments

Fortunately, there have been significant accomplishments in study and treatment of the secondary glaucomas. Improvement of anti-inflammatory agents has reduced the frequency of glaucoma due to inflammation, and advances have been made in studies of the role of prostaglandins in inflammation and secondary glaucoma, in exfoliation glaucoma, in hemolytic glaucoma, and in neovascular glaucoma. These are covered in greater detail in the following

section, Research Needs and Approaches, on the specific types of secondary glaucoma.

Research Objectives

- Determine the causes of the various forms of secondary glaucoma
- Define the role of prostaglandins in secondary glaucoma
- Develop better means of preventing and treating secondary glaucoma

Research Needs and Approaches

Uveitis and Secondary Glaucoma

Uveitis as a cause of secondary glaucoma occurs in many different forms, and a great deal has been published on this subject since 1970. However, with the exception of research on experimentally induced uveitis in animal eyes, and an occasional clinicopathologic report, most of what has been published consists of clinical case reports in which the presence of secondary glaucoma is described but seldom with any inquiry into its cause.

Research has concentrated primarily on animal experiments in which prostaglandins and related substances have been used to produce inflammatory reactions resembling acute uveitis which cause a sharp rise of intraocular pressure. These experiments have raised speculation that prostaglandins and related compounds may have a role in human uveitis and secondary glaucoma.[59]

There is a large literature on the effects of prostaglandins on the eyes of subprimates and nonhuman primates which has examined influences on intraocular pressure but which is primarily focused on the biochemical aspects of the formation, reactions, and fate of prostaglandins in the eye.[59-62] There have also been many experiments to evaluate the effectiveness of prostaglandin antagonists. It is now evident that there are important species differences in response to prostaglandins: rabbits, for example, are much more reactive to this class of substances than are nonhuman primates.[63,64] Since there is little information on how prostaglandins act in human eyes, it is most important to determine whether prostaglandins may be involved in the various types of human uveitis and secondary glaucoma. So far, based on small numbers of cases, there have been claims that the prostaglandin content of the aqueous humor is elevated in Behçet's disease and in glaucomatocyclitis crisis and that treatment with high doses of indomethacin is beneficial in these conditions.[65] Also, there is clinical evidence that the increase in protein content of the aqueous humor after paracentesis can be partially suppressed by administering drugs, such as aspirin, that have antiprostaglandin action.[66] It is hoped that research now being supported will demonstrate conclusively whether or not prostaglandins have an etiologic role in glaucoma.

More investigations are needed to explain why pressure is elevated in some cases of uveitis and not in others. In cases where ocular tension is normal, it would be useful to know whether in some cases this is actually due to subnormal rate of aqueous humor formation that may prevent a rise in pressure despite increased resistance to aqueous outflow.

Apart from obstruction of the angle by synechias, or by angle-closure secondary to sealing of the pupil, it is not really known what occurs in the

aqueous outflow channels (or in the ciliary body) to account for any of the secondary glaucomas associated with uveitis. It is not known whether in uveitis the intrinsic cells of the aqueous outflow system become critically altered or whether cells that infiltrate the ciliary body and aqueous outflow system account for changes in the rate and character of aqueous humor formation and in facility of outflow.

Clearly, there is need for more research on glaucoma secondary to uveitis. However, it is a difficult area for research; several decades of intense effort have not elucidated the mechanisms underlying uveitis. Clinicopathologic study of aqueous humor and tissue samples removed during surgery as well as closer study of the associated aspects of aqueous and vascular dynamics are obvious approaches. In addition, there should be more study of uveitis experimentally induced in primates, possibly starting with methods developed in subprimates.[60,71]

Despite prior failures to gain a better understanding of inflammatory mechanisms in uveitis, further research in this area may lead to understanding of the pathogenesis of the associated glaucoma. Such work may include histocompatibility (HLA) typing, investigations of lymphocyte functions, immunologic characterization of aqueous humor proteins, study of circulating and tissue antibodies, and study of suppression of components of the immune inflammatory response.[72-76] Work is needed on the effects of regulators of phagocytic activity and activation of lysosomal enzymes in relation to the integrity of the aqueous outflow system. Further study is also needed on the role of prostaglandins.

Exfoliation Syndrome and Glaucoma

A significant number of people who otherwise appear to have primary open-angle glaucoma have the exfoliation syndrome.[77] This condition commonly affects a patient's eyes unequally, and it tends to be less responsive to standard medical treatment than primary open-angle glaucoma.[77-80] Testing for responsiveness to corticosteroids suggests that exfoliation glaucoma is not related to primary open-angle glaucoma but that it is one of the secondary glaucomas and has aspects that make it suitable for chemical and histochemical study.[81,82]

If it can be definitely proved that exfoliation glaucoma is not related to primary open-angle glaucoma, this could open up a potentially large and important area for research on its cause. The distinctive clue to the diagnosis and the most obvious lead to research on the cause and possible specific treatment of exfoliation glaucoma is the presence of a fine gray material, resembling dandruff, on the front surface of the lens, back of the iris, and elsewhere in the eye.[77,83-87] Also, in this condition pigment from the pupillary portion of the iris is often scattered to the filtration angle. A clinical study involving a larger number of patients is needed in which clinical diagnoses of exfoliation glaucoma and primary glaucoma are compared with results of corticosteroid response testing.

Further examinations of portions of the aqueous outflow system excised at the time of filtering surgery are required. Comparison of tissue from cases of exfoliation glaucoma with that from cases of ordinary primary open-angle glaucoma can determine whether exfoliation material is present at sites where it would be expected to obstruct outflow. If the exfoliation material identified by slit lamp biomicroscopy and electron microscopy can be clearly implicated as a cause of outflow obstruction in patients or can be demonstrated experimentally to obstruct outflow in enucleated human or animal eyes, this should strengthen considerably what is already an important line of inquiry into the source and mechanism of production of this material. The ultimate aim would be to develop methods for stopping its formation and preventing or alleviating the glaucoma.

Yet, it is uncertain whether this can be achieved. It may be difficult to collect enough material for experimental testing of its effect on aqueous outflow or for chemical analysis, and there is as yet no prospect for an animal model. Human eyes have been known to develop exfoliation after injury or uveitis; these leads might be exploited in searching for a cause or in attempting to develop an animal model.[86] It could prove profitable to reexamine more carefully the chemical constituents, especially the proteins and polysaccharides, of the aqueous humor in this condition. More effort should be expended on chemical analyses of exfoliation material and on studying tissue culture preparations of lens epithelium and other cells associated with exfoliation material in human eyes that are obtained at autopsy. Because there is evidence that the exfoliation material may be partially composed of mucopolysaccharides, the concentration and excretion of mucopolysaccharides and their precursors in the serum of patients who have exfoliation material in their eyes should be investigated. There is also need to study histocompatibility antigens and lymphocytes in the exfoliation syndrome.

Patients with the exfoliation syndrome should not only be studied extensively in the clinic, but they should be made aware of the important contribution they can make to research on this condition by willing their eyes after death for clinicopathologic study.

To date, none of the published research on exfoliation glaucoma has been supported by the NEI despite the magnitude of the problem. Priority should be given to grant applications dealing with this problem.

Hemolytic Glaucoma

In this form of secondary glaucoma, hemorrhage into the vitreous humor or into the anterior chamber produces a severe open-angle glaucoma after a latent period during which fine cells having a characteristic tan color appear in the anterior chamber. These cells have the same color as old blood in the vitreous humor. This form of glaucoma most commonly results from injuries to the eye, but it may also develop as a complication of vitrectomy, the operation used to remove hemorrhages that are associated with diabetic retinopathy[88,89] (see the report of the *Retinal and Choroidal Diseases* Panel, Chapters 2 and 9).

Hemolytic glaucoma responds poorly to standard medical and surgical treatments, especially if there is much of a reservoir of hemorrhage in the vitreous humor. If the amount of blood is small, hemolytic glaucoma can be helped to clear and improve by washing out the anterior chamber with saline solution. In exceptional cases, improvement occurs spontaneously during ordinary medical treatment. It is not a very common form of glaucoma, but it can lead to blindness. Better forms of treatment are therefore needed.

New findings on the cause of hemolytic glaucoma have been made recently through NEI-supported research. It has been found that when red blood cells in an intraocular hemorrhage age, they turn into ghost cells that can severely obstruct the normal drainage of aqueous humor through the aqueous outflow system of the eye.[88] The resulting retention of fluid in the eye causes glaucoma. Fresh red blood cells are very pliable and pass from the anterior chamber out through the aqueous outflow system.[88,90,91] Ghost cells are not so pliable, cannot pass through the outflow system, and interfere with the outflow of aqueous humor. In samples of aqueous humor from patients with hemolytic glaucoma, it is known that minute numbers of macrophages may be present compared to large numbers of ghost cells. In the past, macrophages have been thought to be harmful and obstructive,[92-94] but new evidence indicates that they may have a favorable influence in helping clean up the trabecular meshwork.[95]

Further research is needed to establish conclusively the roles of erythrocyte ghost cells and macrophages in obstructing aqueous outflow and to determine whether fragments of ghost cells can obstruct the outflow system. If they do not, it may be possible to fragment or change the physical character of the ghost cells to relieve the obstruction. Such studies should be done in enucleated human eyes and in an animal model, preferably in monkeys, to determine whether ghost cells or cell fragments obstruct aqueous outflow and how they are handled by macrophages, not only naturally but in the presence of medications that influence the activity of these cells.[96,97]

Lens-Induced Glaucoma

Secondary glaucoma from lysis of the lens (phacolytic glaucoma) and from immune reactions (phacoanaphylactic glaucoma) are relatively uncommon but important forms of the disease that may lead to loss of vision and enucleation if not recognized and properly treated. One of the main problems is to distinguish the various forms of lens-induced glaucoma and to separate them from glaucomas secondary to other causes such as uveitis or intraocular tumor. If the lens is responsible, surgical removal can cure the glaucoma and, if done in time, can restore vision that was thought to have been lost, but if the lens is not responsible, surgical removal is of no avail and may even be harmful.

The most acute and severe form of phacolytic glaucoma occurs with high intraocular pressure in the presence of an open angle.[98-100] Signs of inflammation are present, and vision may be reduced to mere perception of light. In the less acute forms of lens-induced glaucoma, there may be an incomplete cataract or only small fragments of lens left in the eye after incomplete cataract extraction.

Research supported by the NEI has provided evidence that macromolecular lens proteins, without cells, can obstruct aqueous outflow in enucleated human eyes, but whether this occurs in life remains to be determined.[101] It has been known for some time that macrophages swollen with what appears to be lens material are often present in eyes with severe phacolytic glaucoma, but it has not been established whether these cells are responsible for obstructing outflow.[98-100]

Additional research on lens-induced glaucoma of both the phacolytic and phacoanaphylactic types is necessary to clarify some of the fundamental factors in their pathogenesis.

Diagnosis of lens-induced glaucoma may be improved by additional research on methods of examining aspirated aqueous humor to study macrophages and aqueous components that may be important in immune reactions.[102,103] Work is needed to determine whether macrophages actually are helpful by their phagocytic cleaning up of lens debris and might be rendered more effective by drugs that stimulate phagocytic activity. Further investigation is required to determine whether in patients with phacolytic glaucoma, lens proteins themselves may obstruct aqueous outflow.

Specific, noninvasive methods for detecting macromolecular lens proteins in the anterior chamber should be devised for both investigative and diagnostic use. Development of nonhuman primate models of lens-induced glaucoma should be helpful to investigations of the pathogenesis of this condition and to the development of possible new treatments.

Neovascular Glaucoma

This frequently painful form of glaucoma causes a great many cases of visual

loss and occurs as a complication of many diseases in which retinal ischemia is a factor. Once neovascular glaucoma is full-blown, its treatment, consisting of palliative measures or enucleation, has been most unsatisfactory.[104] Research is clearly needed on the pathogenesis and treatment of neovascular glaucoma, particularly study of retinal ischemia as a common causative factor and search for a possible diffusible vasculogenic factor.

Increased research, including controlled clinical trials, is called for on the effects of pan-retinal photocoagulation of the peripheral ocular fundus which, according to preliminary results, appears to have promise for preventing neovascular glaucoma.[105,106] The collaborative study that is being supported by the NEI on the effects of photocoagulation upon diabetic retinopathy provides an excellent opportunity for simultaneous or coordinated investigation of the influence of this treatment on the incidence of neovascular glaucoma.

Research is also called for on the effect of direct laser coagulation of new vessels in the angle before it closes with synechia.[107] More research is needed on possible vasculogenic factors which may stimulate new vessel formation in the iris and angle of the anterior chamber.[108,109] Other research approaches to the problem of neovascular glaucoma that deserve more support include study of histocompatibility antigens in connection with occlusions of the central retinal vessels, genetic factors, responses to corticosteriod testing, and human leukocyte antigen (HLA) categories.

In addition to clinical studies, there should be greater effort to develop animal models of neovascular glaucoma, or at least of neovascularization of the anterior segment. Possibly, an animal model could be developed by induced occlusion of the central retinal vessels or by experimental introduction into the eye of the vasculogenic neoplasms.

Although neovascular glaucoma is acknowledged to be almost untreatable, the *Glaucoma* Panel is optimistic that studies in progress and those which are proposed will lead to a major improvement in the prevention and more effective control at an early stage in the development of this disease.

Pigment Dispersion and Glaucoma

A frequent and enigmatic clinical finding is pigment dispersion from the posterior pigment layer of the iris to the back of the cornea, the front of the iris, and the angle of the anterior chamber. This condition is found mostly in myopic young adults, and in some cases it occurs without elevation of intraocular pressure or other evidence of glaucoma, but in others it is accompanied by open-angle glaucoma.[110,111]

This entity has been called "pigmentary glaucoma," but what its relationship may be to primary open-angle glaucoma, to congenital anomalies of the angle, or to chorioretinal abnormalities is still disputed. This glaucoma can be mild with exacerbations and remissions, or it can be severe enough to require surgery. Miotic therapy, commonly employed in its treatment, is poorly tolerated by young people, and the ophthalmologist is often forced to use less satisfactory means of treatment. Clinical testing of new medications, such as beta-adrenergic blocking agents, may provide better therapeutic alternatives.

Investigations are needed to determine how often people with pigment dispersion, but without glaucoma, are in danger of developing glaucoma, and to determine the fate of young adults with pigmentary glaucoma when they become older. It is important to establish to what extent environmental factors, genetic factors, and treatment influence the course of these conditions. Since pigmentary glaucoma is not common, such studies will have to be performed in centers with large numbers of glaucoma patients.

A few patients with pigment dispersion have been tested for intraocular pressure response to topical corticosteroids, and some tests have been made of glucocorticoid inhibition of transformation of the patients' lymphocytes, seeking relationships to the presence or absence of glaucoma.[112] More investigations like these are needed. The genetic aspects of pigmentary glaucoma need to be established; in particular, relationships to human lymphocyte antigens need to be defined.

In tissues of the aqueous outflow system and portions of the iris that are excised during filtration surgery there should be detailed investigation of the character of the melanin and the behavior of the tissue cells to help clarify to what extent phagocytosis, degeneration of endothelial cells, or changes in the form of the melanin are involved in pigmentary glaucoma.[111,113] This seems important to know because it may be possible to influence this action medically. Because study of biopsy specimens would be useful only for the first part of this investigation, further study in tissue culture would be advantageous. The development of an animal model of pigmentary glaucoma would be even better.

In one series of cases of pigmentary glaucoma, a considerable number of patients were found also to have peripheral chorioretinal degeneration, usually bilaterally.[114] The significance of this finding remains to be determined through additional clinical and histological investigations.

Retinal Detachment and Secondary Glaucoma

Rarely, unilaterial reversible open-angle glaucoma is associated with retinal detachment and is relieved when the retinal detachment is repaired.[115] The pathogenesis of this occurrence is a mystery which if solved could reveal something fundamental about both glaucoma and retinal detachment. Unfortunately, there are no very attractive ideas about how to proceed with such an investigation, except for a suggestion that pigment dissemination is involved. The condition occurs so infrequently that the first step required is a cooperative clinical study involving a number of clinics in order to accumulate a sufficient number of cases and define better the clinical features of the condition.

Epithelial Invasion and Glaucoma

Invasion of epithelium from the outer surface of the eye in the form of a spreading sheet or cystic growth is a serious complication of intraocular surgery and sometimes of accidental penetrating laceration of the eye. It may lead to glaucoma and end with loss of the eye.[116-118] Although uncommon, this condition is serious and surgical excision has only occasionally proven successful. Very little basic research has been done in an effort to improve therapy, and there is no basic understanding of why epithelial invasion almost always takes place in aphakic eyes or in those in which the lens has been injured.[119]

Further research is needed to gain knowledge of the factors that influence intraocular epithelial growth and the mechanisms underlying the associated secondary glaucoma. An animal model for the study of epithelial invasion should prove especially helpful. Such a model would facilitate the investigation of growth-promoting factors and their inhibition and would be valuable for testing possible medical means of treatment. Another approach to be considered would be tissue culture study of surgical specimens from cases of epithelial invasion and examination of the influence of aqueous humor from phakic and aphakic eyes on ocular epithelium growing in culture.

A promising research approach in several of the secondary glaucomas that deserves additional attention is the examination of aqueous humor samples from patients who have glaucoma associated with particles or "flare" in the aqueous humor visible by slit lamp biomicroscopy. Improved methods of examination, utilizing phase contrast microscopy and both transmission and scanning electron microscopy, have made it possible to identify and study cells and particles associated with secondary glaucoma and to correlate these findings with what is seen in tissues of the aqueous outflow system that are excised when surgery for glaucoma must be performed.[88,99,120,121]

Microscopy of aqueous humor samples has already aided diagnosis of epithelial invasion of the anterior chamber, of phacolytic glaucoma, and of hemolytic glaucoma. Biomicroscopic identification in situ of cells and particles in the anterior chamber for diagnostic purposes needs to be improved, possibly by adaptation of specular microscopy to study cellular and particulate precipitates on the posterior surface of the cornea.

It is attractive to consider another related research approach. Large protein molecules which may cause flare in the aqueous may be detected, measured, and characterized by physical methods in aqueous humor samples and then conceivably in patients by analysis of the character of light scattered from a beam crossing the anterior chamber.

Priorities and Recommendations

- Elucidate more fully the mechanisms which precipitate attacks of secondary angle-closure glaucoma
- Establish in human eyes the degree to which prostaglandins are involved in glaucoma secondary to inflammation and injury
- Investigate the fundamental mechanisms of obstruction to aqueous outflow in the secondary glaucomas, especially in those attributable to uveitis, with the aim of developing better treatment
- Clarify the basic mechanism of glaucoma that is associated with the exfoliation syndrome, with the aim of better treatment and possibly prevention of the glaucoma
- Establish conclusively the roles of ghost cells, fragmented cells, and macrophages in glaucoma secondary to intraocular hemorrhages of various types, making use of animal models, with the aim of developing more specific treatments
- Establish the factors that influence intraocular growth of epithelium and the mechanisms responsible for the associated glaucoma, defining the influences of injury or absence of the lens, and making use of tissue culture and, if possible, an animal model
- In studies of neovascular glaucoma, correlate iris fluoroangiographic studies with fundamental experimental research on the stimuli and fundamental mechanisms involved in neovascularization, with emphasis on development of an animal model

- Determine the roles of lens proteins, inflammatory cells, and macrophages in lens-induced glaucoma, utilizing animal models for basic investigations
- Develop more advanced methods for investigative and diagnostic examination of biopsy samples of aqueous humor and anterior segment tissues from patients with glaucoma including the further development of microscopy, tissue culture, chemical analysis, immunologic study, and tests for biologically active substances, such as prostaglandins, and for viruses
- Develop better noninvasive methods for diagnosis of lens-induced glaucoma
- Determine the cause of pigmentary glaucoma and pigment dispersion syndrome

Resource Requirements

Fiscal year 1977 funding for research in the etiology of Secondary Glaucomas will be approximately $331,000 to fund five research grants. The Panel recommends an additional 12 research grants and one specialized clinical research center grant for FY 1976 bringing the total funding in this area of research for that year to an estimated $1,543,000. See the tables at the end of this report for a list of specific recommendations and their associated funding requirements.

2

Optic Nerve and Vision Changes in Glaucoma

THE OPTIC NERVE can be damaged and vision destroyed by every type of glaucoma. In most instances, this is attributable to the effects of an abnormally elevated intraocular pressure.[2,20,122] As yet, there is very little understanding of the manner in which pressure damages the optic nerve[123] and susceptibility to such damage varies considerably among individuals. In some people the optic nerve remains clinically normal for years despite pressures far above normal; in others, the optic nerve becomes severely damaged, and vision is lost, with only slightly elevated pressure.[10,79,122,124-127] And, there is one rare type of glaucoma in which the same optic nerve changes and visual loss occur even without elevation of pressure. This special condition is known as low tension glaucoma.

Because they are the ultimate problem in this disease, optic nerve and vision changes in glaucoma constitute a very important category in glaucoma research. The goal of all efforts to detect glaucoma and to reduce intraocular pressure is to prevent optic nerve damage and consequent loss of vision. Many published studies and much research in progress are concerned with investigation of the optic nerve to gain basic knowledge that is expected to be highly relevant to all forms of glaucoma.[20]

Accomplishments

Properly, this area of glaucoma research has in recent years received greatly increased attention. For a long time, studies of the optic nerve head and changes of vision in glaucoma were purely descriptive. While such studies have continued, there has, in addition, been a considerable growth of research into the cause of glaucomatous cupping and atrophy, particularly research to evaluate the possible effects of intraocular pressure on the blood supply of the optic nerve.

The principal clinical criteria for determining glaucomatous changes in the optic nerve have been observations of a change from physiologic to abnormal cupping of the nerve head and development of defects in the visual fields. But investigators have been slow to recognize the significance of the anatomic configuration of cupping and atrophy of the optic nerve head in terms of changes

in the visual field. This may have been because the detection of early change, and the subtle progression of change, in the cupping and color of the nerve head has long depended upon the experience and skill of the observer.[2,125,128-132] Now photography, used in conjunction with visual field measurements, has been introduced to improve the sensitivity and objectivity of appraisal of optic disc damage as a measure of a patient's progress and as a guide to therapy.

Increased attention to optic disc cupping is important for detection of early changes which can provide valuable forewarning of visual field loss and can signal the need for treatment to reduce the intraocular pressure.[2,20] Clinicians have increasingly recognized that one of the commonest signs of pressure-induced change in optic disc cupping is a difference between the size of the cups in an individual's two eyes.[2,20,133,134] In adults, such asymmetry is rare in the absence of significant glaucoma.

Objective methods of documenting progression in optic nerve head cupping have long lagged behind capabilities for detecting progressive loss of visual field. But stereophotographic equipment has now been devised which can accurately record the appearance of the optic nerve head at successive monthly or yearly intervals. This technique permits more sensitive and revealing comparison of changes over a period of time and is potentially an improvement over ophthalmoscopic means for detecting slight progression of changes in the optic nerve head.[135]

For the purpose of three-dimensional analysis of the optic disc, investigations that use photogrammetry are already underway. This technique converts stereophotos of the disc to contour maps by a tedious and costly process in the hope of improving detection and differentiation of subtle abnormalities.[134,136,137] Such studies need to concentrate on selective locations of damage rather than simple radius or volume measurements. These methods ultimately need to be compared for sensitivity and reproducibility with simple visual means of comparing sequential stereophotographs of the disc.

Research Objectives

- Determine the relationship between intraocular pressure, optic nerve changes, and loss of visual field
- Determine whether some cases of glaucomatous field loss may be reversible
- Clarify the role of the blood supply to the optic nerve head in glaucoma
- Clarify the relationship between systemic blood pressure and intraocular pressure in damage to the optic nerve head
- Evaluate means of predicting the occurrence of glaucomatous field loss in patients with elevated intraocular pressure
- Determine why the optic nerves of some people are more susceptible to damage than others at the same levels of intraocular pressure and elucidate the role of heredity in this variable susceptibility
- Develop means of treating low tension glaucoma and identify factors which may predispose an individual to this condition
- Develop suitable animal models of chronic glaucoma

Research Needs and Approaches

Relationship Between Optic Nerve Head Cupping, Intraocular Pressure, and Field Loss

Relationships between the degree of intraocular pressure and the rate and character of cupping, atrophy, and field loss are very important to consider and investigate. Characteristically, in chronic glaucoma with moderately elevated intraocular pressure, abnormal cupping of the optic nerve head develops slowly and defects in the visual field gradually become evident. However, in acute angle-closure glaucoma, in which the intraocular pressure rapidly becomes very high, the optic disc can be damaged severely without preliminary cupping. This gives rise to an atrophic nerve head without a pathologic cup but with severe loss of vision.[2,124,125,138]

The fundamental difference between the slowly developing effects of common chronic glaucoma and the relatively uncommon severe effect of very high pressure in acute glaucoma presents a problem in studying the pathogenesis of optic nerve head damage in simulated glaucoma. So far, most of the experimental studies that have been done in monkeys or other animals have been of the acute, high pressure, short duration type of glaucoma.[139-142] For future research, a primate model of chronic, mildly elevated pressure is needed which will permit study of the effects on the optic nerve head over a long period. Unfortunately, study of damage mechanisms is far more difficult in a chronic model.

Another very important question is the varying relationship between moderately elevated intraocular pressure and the rate and severity of damage to the optic nerve head among different people. Why there should be such a broad range of individual vulnerability is unexplained. Although it is believed that many optic nerve heads eventually suffer some damage from intraocular pressure above 25 mm Hg, a smaller number have been known to withstand pressures from 30 to 40 mm Hg for long periods without damage.[2,124,125,127] On the other hand, a very small number of people show all the features of glaucomatous cupping, atrophy, and visual field loss with intraocular pressures of 20 mm Hg or less.

Establishing primate models of chronically elevated intraocular pressure should help determine whether there is a corresponding spectrum of susceptibility among subhuman primates, and if so, why. The influence of systemic blood pressure could be studied, among other things.

Reversibility of Cupping and Field Loss

One of the most intriguing aspects of optic nerve cupping and loss of visual field in glaucoma is that when, in occasional cases, intraocular pressure is reduced to normal or below normal levels, abnormal cupping of the nerve head can dramatically disappear and visual field can appreciably improve.[2,3,125,143-145] This occurs most frequently in children, but occasionally it is seen in adults.[146] If in children with glaucoma and conspicuously abnormal optic disc cupping, surgery is successful in reducing the intraocular pressure to normal or below, cupping can improve within hours or days to a semblance of normal.[147]

The same effect can occur in adults but is increasingly rare with advancing age and recovery is probably slower. Optic nerve atrophy does not improve, but a nonseeing portion of the visual field can regain some visual function when the intraocular pressure is reduced

These phenomena have to be considered seriously in any attempt to explain the influences of intraocular pressure on the optic nerve and vision. They suggest that elevated intraocular pressure may directly influence the form of the optic disc or the water content of the disc tissues in some manner that is rapidly reversible when the pressure is reduced. The reversal that is seen clinically seems too rapid to be explained by proliferation of disc tissues.

These phenomena also suggest that part of the loss of field induced by elevated pressure is in some cases functional and is reversible when excessive pressure on the optic nerve fibers is relieved. Such an effect may be distinct from the permanent visual loss associated with the death of nerve fibers that characterizes optic nerve atrophy in glaucoma and in other eye diseases that do not involve elevated intraocular pressure.[148]

Research should be directed toward clarifying the way in which the optic disc may be deformed and its function impaired, either reversibly or irreversibly, in relation to elevation and reduction of intraocular pressure. This requires not only systematic clinical study and evaluation but the creation of a subhuman primate model in which optic nerve changes in response to induced variations in intraocular pressure can be studied. In such a study, it may be important to maintain pressure in the eye while histologic fixation of the optic nerve head is performed. This may help preserve significant features of nerve head configuration that may be altered or lost when, in the customary manner of fixation, the eye is allowed to go to zero pressure. A similar investigation of maintaining pressure during fixation has shown that changes occur in the configuration of the aqueous outflow system of human and monkey eyes at different intraocular pressures.

Blood Supply

In the study of the etiology of optic nerve head cupping and atrophy in glaucoma, much research on anatomy,[150,153-157] blood circulation,[140,155,158-162] and axoplasmic flow in the nerve fibers[163-167] is being carried on. This work offers promise that the problem will ultimately be solved, but there is still no explanation of the pathogenesis of changes in the optic nerve in glaucoma. Some investigators have believed that fluid pressure and sliding of the laminae of the lamina cribrosa could simply distort the nerve physically, but a large number of publications in recent years attest to a widespread belief that the blood supply to the nerve head is somehow critically involved in its damage in glaucoma.[123,149-152] Studies of this blood supply have provided some information about the anatomy, physiology, and experimental pathology of the nerve head circulation, but they have not yet provided a description of the pathogenesis of the changes encountered in glaucoma patients or much of predictive or therapeutic value. New and ingenious approaches are needed for the study of this relationship.

A number of diseases other than glaucoma, some involving the blood vessels of the optic nerve, also cause optic nerve atrophy, but if the intraocular pressure is not elevated, optic nerve head cupping rarely develops. This observation makes it difficult to explain the changes in the optic nerve in glaucoma entirely on the basis of interference with blood supply. However, an observation has been made recently that may help bridge the gap. It has been pointed out that the optic atrophy produced by temporal arteritis can in some cases be different from other types of atrophy. Peculiarly, after several months, this condition can be accompanied by development of cupping that closely resembles glaucomatous cupping, though the intraocular pressure is not elevated.[151,168] However, the effect on vision is different from that in glaucoma in that central vision is lost early rather than tending to survive.

Role of Systemic Blood Pressure

There is a real and very practical question concerning the relationship of systemic blood pressure to the vulnerability of the optic disc in glaucoma.[148,160 169-172] Anecdotal case citations suggest the possibility of a significant relationship, but there is need for a planned, systematic appraisal and for an assessment of whether reducing pathologically elevated blood pressure increases the susceptibility of the optic nerve to damage by elevated intraocular pressure. This information would be important for guiding internists in deciding to what degree they should seek to reduce the blood pressure of patients who have not only systemic hypertension but increased intraocular pressure. This subject presents problems of sufficient technical complexity that a task force might be necessary to plan how this investigation might realistically be undertaken. Prospective, controlled clinical research is needed to evaluate the risk to vision in glaucoma from treatment of systemic hypertension.

Predictive Factors

Some means of detecting and predicting in each individual case the susceptibility of the optic nerve head to damage by a given degree of elevation of intraocular pressure is greatly needed. Potential acute test methods have been explored, for instance, determining the degree of intraocular pressure elevation required to induce a transitory scotoma in a Bjerrum area. These studies have shown that this could be accomplished at lower pressures in eyes with the disc already damaged by glaucoma than in those of normal people.[155,160,173-175] Clinical studies should be planned in which such tests are applied soon after elevated intraocular pressure has been detected and the results compared with the patient's vision years later to determine whether the tests can help predict how much pressure the optic nerve can stand over a long period of time. Difficult though this may be to establish, a reasonably reliable predictive measure of the optic nerve's vulnerability could provide an extremely valuable aid to the ophthalmologist who must decide when and how intensively to start treatment of an individual with elevated intraocular pressure. The long-term results of using such a procedure would have to be compared with those in cases where treatment was not initiated until the first abnormal change in nerve head cupping was detected.

Improved Visual Field Testing

Studies of the reliability and reproducibility of visual field testing may be clinically useful. Present difficulties in achieving systematic and reliable visual field testing in everyday practice make improved automatic methods seem desirable, although what is desired may be difficult or impossible to achieve. Yet, it is an important area for research because at present the lack of good visual field information hampers many clinical decisions.

Low Tension Glaucoma

Low tension glaucoma appears to be at one important end of the spectrum of ordinary glaucomas in which the optic nerve is extraordinarily susceptible to cupping and atrophy when the intraocular pressure is only in the upper portion of

what is usually considered the normal range. This is in contrast to eyes at the other end of the spectrum in which there is extraordinary resistance to cupping and atrophy despite considerable elevation of intraocular pressure.[2,176]

Though not very common, low tension glaucoma is of great importance for general understanding of the nature of optic nerve damage in glaucoma. The cause and treatment of low tension glaucoma is one of the problems in glaucoma most seriously in need of more research. This disease needs study not only for the sake of people losing vision from it, but for providing better understanding of the mechanism of optic nerve damage that occurs in ordinary glaucoma. Because low tension glaucoma is a human condition without known counterpart in animals, clinical research on this condition is needed and such studies must be much more comprehensive than anything done in the past.

Publications concerning low tension glaucoma since 1970 provide hints that an abnormality of blood supply to the optic nerve is involved.[177–179] However, there has been no truly comprehensive study of the problem and no specific project supported by the NEI, though a small number of preliminary observations have been made with NEI support. Much more thought and research should be devoted to the problem of explaining low tension glaucoma. Among these are the following:

- Investigation of the relationship of low tension glaucoma to local and systemic blood pressure
- Investigation of the blood circulation of the optic nerve head in relation to the intraocular pressure (IOP) by the best and latest methods
- Investigation of the characteristic level and variation of the IOP
- Evaluation of the influence of reducing the IOP, particularly to very low levels by surgery in one eye to ascertain if this arrests the process as it seems to have done in a small number of cases
- Investigation of the degree to which the condition occurs bilaterally
- In exceptional unilateral cases, a particularly thorough comparison of all measurable parameters of the two eyes
- Investigation of the genetic aspects, particularly the role of corticosteroid responsiveness and HLA antigens
- Study of orbital as well as ocular blood circulation
- Investigation of relationships to present or past systemic or neurologic diseases or circulatory disturbances
- Investigation of the relationship of low tension glaucoma to age

Home tonometry should be utilized as extensively as possible when investigating individuals who may have low tension glaucoma. This can help establish conclusively whether their intraocular pressure remains within the normal range at all times, since this is an essential criterion in diagnosing this form of glaucoma.

There is reason to believe that a breakthrough in understanding low tension glaucoma would increase comprehension of the vision-destroying effects of glaucoma in general.

Other Needs

There are many other clinically pertinent questions that can be answered only

by long-term, collaborative clinical trials perhaps involving extensive training or reeducation of the collaborating investigators. Is it legitimate to wait until field loss occurs before instituting treatment, or should treatment be started as soon as abnormal progressive cupping is established? Should older patients with abnormal pressure but with normal discs be treated, but should younger patients be left untreated for a decade and then treated (to avoid side effects of chronic therapy)? These and many more important questions seem to be answerable but only with great effort and expense.

Increasing attention is being given to the possibility that the susceptibility of an individual's optic nerve to damage by intraocular pressure may be genetically determined and that correlations may be found between various genetic markers and the degree of susceptibility. Preliminary reports of HLA typing and responsiveness of intraocular pressure to topical epinephrine need to be validated by thorough study by several independent groups of investigators. This is urgently required.

Priorities and Recommendations

- Document by serial stereophotography the character and type of long-term progression of cupping and atrophy of the optic nerve head and correlate these findings with the occurrence and progression of changes in the visual fields of patients with glaucoma.
- Develop a primate animal model of chronic glaucoma for lifelong investigation and stereophotographic documentation of changes in the appearance of the optic nerve head for subsequent correlation with histopathology. With a sufficient number of animals, explore how much individual variation there may be in susceptibility of the nerve head to injury by a given pressure.
- Perform prospective, controlled clinical research to evaluate the risk to vision from treating systemic hypertension in patients with glaucoma.
- Determine through long-term clinical evaluation the predictive value of factors that may indicate the susceptibility of different optic nerve heads and visual fields to change under the influence of chronically elevated intraocular pressure.
- Compare the prevalence and severity of primary open-angle glaucoma among different races and anthropologic types, with special attention to Black populations.
- Compare the efficiency of visual evaluation of serial stereophotographs for detecting optic nerve head changes in glaucoma with that of photogrammetry and direct ophthalmoscopy.
- Perform clinical investigation and stereophotographic documentation of the rapidity and reversibility of glaucomatous cupping of the optic nerve head and change in visual field after intraocular pressure is reduced to a low-normal level. Parallel investigation of the reversibility of pressure-induced cupping in a primate model of chronic

glaucoma as a preliminary to research on the mechanism should also be pursued.

- Perform clinical research on low tension glaucoma to evaluate the influence of reducing the intraocular pressure, particularly to very low levels by surgery in one eye, to ascertain if this arrests the progress of the disease.
- Perform clinical research on low tension glaucoma aiming to identify factors that may be peculiar to or predispose an individual to low tension glaucoma, although there are now very few clues to begin such a study.

Resource Requirements

In FY 1977 there will be approximately 14 research grants and one research contract in the subprogram *Optic Nerve and Vision Changes in Glaucoma*. Estimated funding for these will amount to $930,000. The Panel recommends an additional four research grants, one specialized clinical research center, and one research contract which will bring total NEI funding of this subprogram to approximately $1,699,000 in FY 1978. See the tables at the end of this report for specific recommendations.

3

Hydrodynamics of the Eye

EXCEPT FOR SO-CALLED low tension glaucoma, elevation of the intraocular pressure is the common denominator of all the clinically characterized, different types of glaucoma. Excessive intraocular pressure is the most widely recognized cause of damage to the optic nerve and impairment of vision in glaucoma. The hydrodynamics of the eye must be studied to learn what factors underlie the normal regulation and failures of regulation of intraocular pressure. There must be inquiry into relationships among aqueous formation and outflow, the effects of blood supply, and the anatomy, physiology, pharmacology, and pathology of the hydrodynamics system of the eye. The more that is learned about ocular hydrodynamics, the better the clinical features of glaucoma and how to treat it will be understood.

Research on ocular hydrodynamics is most commonly carried out in animal and human eyes, postmortem as well as in life. Investigations of the physiology and pharmacology of ocular hydrodynamics can often be carried out in normal animals and in normal and glaucomatous human eyes. Important information has been developed during the past hundred years, but improved research methods heighten anticipation that important new knowledge will be gained in the future.

Since 1970, a large proportion of experimental research on hydrodynamics of the eye has been supported by the National Eye Institute, and this is a category which deserves still more support through research project grants.

In the National Advisory Eye Council's program planning report of 1975, emphasis was placed on encouraging investigations of the mechanisms of production and outflow of aqueous humor in primates and man. Specific attention was given to the need for additional research on the fundamental mechanisms of aqueous humor formation, the pathways for aqueous humor egress, and the factors responsible for regulating intraocular pressure. The report indicated need for a search for noninvasive methods for studying aqueous outflow.

The report also stated that there was great need to attract interest in and to encourage pharmacologic and physiologic studies in the subhuman primate and, more importantly, in man. It was recommended that the mechanism of aqueous formation and the possibility of the presence of a chloride pump should be further investigated. Additional studies of aqueous outflow mechanisms in animals and especially in man were encouraged. It was recognized that this required the development of the necessary clinical research environment and well-trained

investigators to bring better understanding of regulation, behavior, dynamics, and effects of ocular pressure. These principles and recommendations still hold true.

Accomplishments

Research on ocular hydrodynamics in relation to glaucoma has involved many of the leaders in ophthalmology during the last hundred years. Their studies have advanced from the earliest recognition that intraocular pressure elevation is a prominent feature of glaucoma to the present understanding that the main determinants of pressure are the rate of aqueous humor formation, the resistance of aqueous outflow, and the recipient venous pressure. Furthermore, it is now understood that most forms of glaucoma are due to obstruction of aqueous outflow.

Many details have been discovered concerning the secretion-diffusion manner of aqueous humor formation, the properties of the aqueous outflow system in primates particularly, the effects of pharmacologic agents, and the influences of innervation and blood circulation. Anatomic and pathologic studies have shed light on some of the causes of outflow obstruction. Yet, despite this work of a century and more, it is remarkable how many truly key parts are still missing that will be essential to full understanding and complete control or prevention of glaucoma.

Research Objectives

- Clarify the mechanism of aqueous humor formation and factors that govern it
- Ascertain the manner in which aqueous humor leaves the eye via Schlemm's canal and how resistance to outflow may be influenced
- Assess the significance of uveo-scleral routes for escape of aqueous humor in human eyes in relation to glaucoma and its treatment
- Explain the influence of uveal fluid on aqueous formation
- Determine the basis for circadian variations of intraocular pressure in glaucoma and see whether an innate mechanism for periodic subsidence of pressure may be exploited therapeutically
- Characterize the properties and behavior of the vitreous humor that are involved in certain forms of angle-closure glaucoma

Research Needs and Approaches

Formation of Aqueous Humor

The rate of formation of aqueous humor and aqueous outflow are the prime determinants of the level of intraocular pressure. For better understanding and better treatment of all types of glaucoma, it is essential that more be learned about the mechanisms of aqueous humor formation and the physiologic, pathologic, or pharmacologic factors that may control it.

The role of prostaglandins in aqueous formation has been of particular interest in recent research.[59,62] Prostaglandins and related compounds have been found to raise the intraocular pressure in rabbit eyes by causing increased inflow of fluid into the eye, vasodilation, and breakdown of the blood-aqueous barrier. The responses in rabbits so resemble inflammatory reactions to injury that a considerable portion of research done on prostaglandins in the eye has been coupled with research on the action of irritative conditions or injurious substances. Several such factors have been shown to induce elevated pressure in rabbit eyes, in part through the mediation of prostaglandins formed in the eye in response to these stimuli and in part through innervational stimuli.[180-190]

These intraocular pressure responses have been shown to be partially prevented by prostaglandin-antagonist drugs such as aspirin and indomethacin.[66,190-195] These studies have raised the question of to what degree the glaucomas that develop secondary to injury or inflammation in human eyes might be mediated by prostaglandins.[59] However, investigations comparing rabbits and monkeys indicate that the eyes of primates may be considerably less responsive to prostaglandins and may have less tendency to form prostaglandins in response to irritation or injury.[63] Much further research is required not only in testing for these substances but in evaluating to what degree prostaglandin-antagonist drugs may be useful in treating humans with uveitis and secondary glaucoma.[65,71]

With the ultimate aim of applying new information to clinical problems, it is more desirable to study aqueous humor formation in primates rather than in subprimates, except for certain investigations in which clarification of species differences may be of particular interest. Formation of aqueous humor in monkeys can be studied by invasive methods that are reasonably satisfactory, but for humans, noninvasive methods are needed. So far, most measurements in humans have been made by utilizing fluorescein turnover or by indirect tonographic or perilimbal suction cup methods.[196-202] Invasive methods that were originally developed for animal studies involving aqueous perfusion or monitoring the rate of disappearance of injected radioactive albumin from the anterior chamber have been used in special circumstances in humans, but noninvasive methods are preferable.[203-205] More comparisons should be made among the clinically applicable methods to help in assessing their validity, and more comparisons should be made among invasive methods in monkeys.

There is a clear need for reliable studies to compare patients with glaucoma with normal individuals to establish better the interrelationships between aqueous formation, intraocular pressure, and aqueous outflow. But, the main problem to be overcome is how to establish direct but noninvasive means for measuring and monitoring aqueous formation. Further evaluation may show present indirect methods to be reliable, but so far their complexity has limited their use to a few highly specialized laboratories. A good, clinically applicable method could make possible more intensive and revealing research on homeostatic mechanisms, circadian pressure variations, actions of medications, and effects of disease states and could help in determining whether aqueous flow is necessary to keep outflow channels open. Until a more ideal method is developed, greater use of improved fluorescein turnover methods will permit progress to be made in the study of human aqueous humor flow.[199-202]

Further fundamental research is required on the influence of intraocular pressure on the various parameters of ocular hydrodynamics, particularly to distinguish the influence of intraocular pressure on aqueous humor formation from its influence on facility of outflow.[197,198] Research is also needed on the relative roles of secretion and ultrafiltration in aqueous humor formation.[206]

Additional research is required on the influence of blood flow in the ciliary processes on aqueous humor formation. It is likely that intraocular pressure

affects aqueous formation in part by influencing the rate of blood flow through the ciliary processes.[207] It is hoped that research in this area will help clarify whether pseudofacility results when elevated intraocular or venous pressure interferes with ciliary blood flow, or whether it results from a decrease in ultrafiltration induced by intraocular pressure elevation, or both.[197,208] Further research is needed to determine to what degree control of ciliary blood flow may influence production of aqueous humor. Methods are available for nonhuman primate studies of blood flow in the ciliary body, but there is need for a valid, noninvasive, and safe method for measurements in humans.

There is also an urgent need to clarify the mechanism of aqueous humor formation, particularly in the eyes of humans and nonhuman primates and especially with respect to the metabolic processes involved. There is need to define the role of the ciliary epithelial cells and explain the mechanism of action of adrenergic agents, circulating hormones, and pharmacologic agents such as the carbonic anhydrase inhibitors and cardiac glycosides. Also, the influence of blood composition on aqueous humor formation needs to be elucidated, particularly in relation to the action of carbonic anhydrase inhibitors. The mystery of why topically administered carbonic anhydrase inhibitors fail to reduce aqueous formation requires investigation and clarification.[209-212] In general, research to obtain a complete understanding of the carbonic anhydrase inhibitors on aqueous humor formation should have high priority. This understanding should provide important insight into the physiology of aqueous formation and may lead to the development of improved means for medical reduction of intraocular pressure. Effects of carbonic anhydrase inhibitors on blood flow must be differentiated from their effects on ion transport in the ciliary body.

Research concerning pharmacologic influences on aqueous humor formation, apart from research on the prostaglandins, has usually been preoccupied with a search for substances which reduce the rate of aqueous humor formation and which have possible use in treating glaucoma; but, it is evident that there is also need to search for substances which may increase the rate of aqueous humor formation. These could be useful in treating excessive hypotony and should be particularly applicable in studies of uveo-scleral functional relationships when, as in the case of choroidal detachment, aqueous humor appears to be depressed. Such substances might even be helpful in elucidating the mechanism of low tension glaucoma.

Outflow of Aqueous Humor

Anatomical studies of the aqueous outflow system until recently have suffered from failure to appreciate that when histologic fixation is carried out with zero intraocular pressure and with no flow, as has long been customary, the microscopic configuration of the tissues is significantly different from what is seen when fixation is carried out with pressure and flow the same as in life, or as induced during experimental procedures.[213-219] Even when standard histologic fixation of the aqueous outflow system is performed under physiologic conditions of pressure and flow, the fixation procedure artifically raises the resistance to aqueous outflow. More studies of the anatomy and physiology of the outflow systems are needed, but when comparing normal eyes and eyes with glaucoma, it is of prime importance to take into account or, if possible, to eliminate the artifacts induced by fixation. Similarly, in relating function and physiology to pathology, as in studies of mechanisms of the secondary glaucomas, there is need to control the conditions of histologic fixation.

In human and monkey eyes it has been shown that when the intraocular pressure is raised and the flow through the aqueous outflow system is increased,

portions of this system change in shape with the juxtacanalicular endothelial meshwork distending and Schlemm's canal narrowing.[213-222] These changes in configuration are reversible within minutes when the pressure and flow are reduced.[223] Also, it has been determined that in normal human eyes postmortem, when pressure and flow are artificially elevated, resistance to flow through the aqueous outflow system is raised.[224,225] In glaucomatous eyes postmortem, this phenomenon may be more pronounced than in normal eyes. A quite different effect has been found in the eyes of living monkeys perfused for several hours at elevated pressure. This causes dramatic decrease of outflow resistance and morphologic changes in the outflow system, all spontaneously reversible in a few days. These contrasting effects urgently call for clarification.[226,227]

Considerable attention has been given to the physical aspects of aqueous outflow. This includes presentation of evidence that the action of miotic drugs, such as pilocarpine, used in the treatment of glaucoma may exert their pressure-reducing action physically by causing the ciliary muscle to contract and pull on the scleral spur and aqueous outflow channels so that resistance to flow is reduced. Research on human eyes postmortem has shown that a force applied through the ciliary muscle to the scleral spur and trabecular meshwork reduces resistance to outflow. The effect is reversible when the force is reduced.[90,228,229] Also, in monkeys in which the ciliary muscle has been detached from the scleral spur, pilocarpine has no effect on aqueous outflow.[230] Modulation of aqueous outflow by the ciliary muscle clearly is important and requires more detailed investigation.

Electron microscopic studies of the aqueous outflow system in monkey eyes and the use of tracer substances have provided intriguing suggestions of the detailed routes that the aqueous humor may take in escaping from the eye. They have also provided information on a mechanism that lets erythrocytes pass from the anterior chamber to Schlemm's canal, but not readily in the reverse direction, though finer particles apparently can go in either direction.[95,96,231-236]

Although these investigations into the physical aspects of and physical responses and controls over aqueous outflow seem to have increased understanding of how pilocarpine works in treating many glaucomatous eyes, they have left unexplained the action of drugs such as epinephrine which can also reduce resistance to outflow but have no obvious physical basis for their action. Very important questions have been raised concerning the importance of physical phenomena as compared with that of metabolic processes in controlling aqueous outflow.[95,214,223,237-239] This is an enigma that needs to be resolved.

Studies of the influence of temperature on aqueous outflow in eyes postmortem have indicated that physical rather than metabolic factors predominate, yet it is difficult to account for the action of epinephrine or a number of other substances on aqueous outflow without invoking the importance of vital metabolic processes.[240] Particularly impressive has been a demonstration that the hormone-like substance cyclic AMP has an action on the aqueous outflow system in animals that is probably closely related to or that mediates the action of epinephrine and other catecholamines.[241-243] The latter lose most of their effect after death.

Metabolic studies of the tissues that lie between the anterior chamber and Schlemm's canal, particularly those closest to the canal that are thought to have the greatest influence on aqueous outflow, are overdue. Clarification of how these tissues respond to drugs and hormones is important to the understanding of the role of metabolism or vital activity in modulating aqueous outflow, of the mechanism underlying corticosteroid glaucoma, and of the manner in which adrenergic drugs, cyclic AMP, and hyaluronidase influence aqueous outflow in normal eyes and, even more significantly, in glaucomatous eyes. Studies are needed not only in animals and in excised eyes but also in cultures of tissues

obtained at the time of surgery or postmortem.[244] Possibly most attractive is the study of specimens of human trabecular meshwork in tissue culture. This will permit systematic metabolic comparisons of normal and glaucomatous tissues, particularly investigation of mucopolysaccharides which were brought into consideration years ago by studies of the effects of hyaluronidase on aqueous outflow in animal eyes and more recently have been postulated to play a part in the development of corticosteroid glaucoma.[245-248] Enzymes involved in production and destruction of mucopolysaccharides need to be studied, and means for modifying their function in animal eyes need to be tested. Research is required to identify target tissues or receptors in the eye for hormones such as the catecholamines, corticosteroids, and cyclic AMP. Such studies, if successful, would be a step toward explaining change in resistance to outflow on a molecular basis.

It is important to study eyes as soon as possible after enucleation or dissection to determine whether cellular metabolism plays a significant role in determining outflow resistance.[95,214,223,239] Research is needed to demonstrate whether eyes obtained postmortem are still metabolically active, for instance to determine whether the endothelium incorporates labeled thymidine and whether the rate of oxygen uptake or lactic acid production by the trabecular meshwork relates to facility of aqueous outflow. There is obvious need to clarify the degree and manner in which metabolic and enzymatic activities of the outflow system participate in regulating (facilitating or obstructing) aqueous outflow with the prospect of ultimately gaining control of these interactions for therapeutic or even prophylactic purposes.

Study of obstruction of the aqueous outflow system by specific cellular or particulate materials or poisons should help explain the mechanism of various types of secondary glaucoma as well as increase understanding of the physiologic process of aqueous outflow. Improved techniques for artificially obstructing the aqueous outflow system may provide animal models for study of the effects of elevated intraocular pressure on the optic nerve and other ocular structures.

Beyond the trabecular meshwork and inner wall of Schlemm's canal, the relationships of the walls of the canal to one another and the properties of the collector channels and extraocular venous system merit study. The characteristics of blood reflux into Schlemm's canal in normal and glaucomatous eyes, and the episcleral venous pressures associated with vasculopathies, various types of glaucoma, and antiglaucoma surgery require further investigation. More reliable, clinically applicable methods of investigation are required for comparisons of aqueous outflow in normal eyes with those that have glaucoma.

Uveo-Scleral Functional Relationships

There are two highly intriguing and little-studied aspects of the uveo-scleral relationship in the region of the ciliary body that call for more research. One is the so-called uveo-scleral outflow, studied mainly in rabbits, monkeys, and dogs, in which a fraction of the aqueous humor from the anterior chamber passes through the anterior end of the ciliary muscle to the choroid and sclera, independent of intraocular pressure, but dependent on the degree of compactness of the ciliary muscle.[249-254] The other functional aspect of the relationship of the ciliary body to the sclera is revealed almost entirely through clinical observations. Ophthalmologists are familiar with the fact that a layer of fluid interposed between the ciliary body and sclera interferes with aqueous humor formation and reduces intraocular pressure. This is well-known clinically as a manifestation of choroidal detachment, choroidal effusion, and cyclodialysis.[255,256] Choroidal detachment is known to be induced by low intraocular

pressure, consequent to a leaking wound or excessive filtration after antiglaucoma surgery.[255]

The rate of aqueous humor formation is reduced by detachment of the choroid and ciliary body without an artificial communication from the anterior chamber to the suprachoroidal space and also by cyclodialysis which does provide a communication. What relationship, if any, this bears to so-called uveo-scleral flow remains unknown.

Little is known about uveo-scleral flow in human eyes. Dyes and fine particles have been traced via the uveo-scleral route in experiments postmortem, but quantitative evaluation in vivo is wanting.[257–260]

More research is needed to determine the clinical significance of the uveo-scleral flow and, probably more importantly, to explain how detachment of the choroid and ciliary body reduces aqueous humor formation. This has a very practical aspect because choroidal detachment with hypotony is an unwanted complication of filtration surgery and occasionally of surgery for cataract. Improved means of preventing or treating this complication are needed. Furthermore, elucidating this phenomenon could provide new and better approaches to controlling elevated intraocular pressure in glaucoma and might provide a better understanding of how to treat excessive hypotony following intraocular surgery. More research on this phenomenon is clearly needed; a good animal model would be valuable.[261]

Studies of the chemical composition of the uveal effusion fluid in choroidal detachments in human eyes (without cyclodialysis) have shown the presence of proteins of the same type found in blood, but with less of the larger molecules than of the smaller, which suggests a sieving effect.[262,263] Possibly more intriguing is that the ascorbic acid concentration in the fluid has been found to be low like that of blood, rather than high as in the aqueous humor. This suggests that a significant portion of choroidal detachment fluid does not come from the anterior chamber.[263]

Circadian Variation of Intraocular Pressure

Spontaneous variation of the intraocular pressure in open-angle glaucoma remains one of the most important and least understood enigmas of glaucoma.[264–268] There is need to establish whether variation in intraocular pressure is attributable to variation in aqueous humor formation or to change in resistance to aqueous outflow. There is also need to compare spontaneous variation of intraocular pressure in different types of glaucoma. In some patients with open-angle glaucoma and severely obstructed aqueous outflow, the intraocular pressure periodically decreases to the normal range.[269] There is evidence that this is due to a spontaneous decrease in aqueous humor formation (hyposecretion) which reduces the pressure even though resistance to outflow remains high.[20,270] This phenomenon seems to be of great importance in glaucoma research, not only for basic understanding but because of the possibility it suggests for exploiting a natural mechanism to achieve better control of intraocular pressure. Further investigations are required to determine possible hormonal, neural, or hypothalamic influences. Fluorescein turnover or other methods of measuring aqueous formation might be employed. It is very likely that such studies would have to be carried out in glaucoma patients in whom variations in intraocular pressure are larger than in normal individuals. Factors which may interfere with the rhythm of spontaneous remission of elevated intraocular pressure should be thoroughly examined.

So far, there appears to be no promising animal model for this research. A noninvasive clinical device for constantly monitoring intraocular pressure would

be particularly useful in conjunction with methods for measuring the rate of aqueous flow. Devices have already been developed (with and without NEI support) which are capable of noninvasive radio monitoring of intraocular pressure in animal eyes, but the goal is an instrument for use with glaucoma patients that is comfortable, can be tolerated for a long time, and is capable of making precise measurements.

Advantage should be taken of the fact that groups of scientists who are not engaged primarily in eye research, neuroendocrinologists in particular, are carrying on clinical studies of different circadian rhythms. Efforts should be made to establish collaborative investigations in which variations in intraocular pressure may be correlated with the neuroendocrine factors already under study.

Vitreous Humor Barrier Properties

More research is required on the characteristics of movement of fluid through the vitreous and across the vitreous face,[271,272] particularly in relation to mechanisms influencing the depth of the anterior chamber. More knowledge is needed of how these properties vary among normal and abnormal eyes, their implications for surgery, and their role in the shallowing of the anterior chamber after choroidal detachment, pan-retinal photocoagulation, and occasionally after central retinal vein occlusion. There should be more research to define how vitreous volume responds to hydrostatic and osmotic pressure when the anterior chamber shallows in response to miotics and in the more extreme case of malignant glaucoma when the anterior chamber flattens. The relationship between aqueous humor flow and vitreous distention pressure should be clarified, and more study is needed to establish the functional, physical, and biochemical character of the vitreous humor and its anterior limiting membrane in normal and abnormal eyes. Studies in enucleated human eyes and possibly in nonhuman primates are indicated.

In addition to the foregoing areas of ocular hydrodynamics, there are more specific topics which would profit by further research. These include additional intensive study of the action of adrenergic compounds and their potential toxicity to the macula. Investigation is also required of the modulating of intraocular pressure that may be exerted by innervational and hypothalamic influences.

Priorities and Recommendations

Formation of Aqueous Humor

- Develop better noninvasive means for measuring and monitoring the rate of aqueous humor formation in monkeys and in humans. This would facilitate several important lines of clinically-applied glaucoma research.
- Conduct research to improve understanding of the action of carbonic anhydrase inhibitors on aqueous formation, and explain why they fail to reduce aqueous formation when administered topically. Effects on blood flow must be differentiated from effects on ion transport.
- Search for substances to increase the rate of aqueous formation which could be applied to treatment of excessive hypotony such as that associated with choroidal detachment.

Outflow of Aqueous Humor

- Ascertain the relative influences of physical factors and of metabolic processes, as well as the manner in which catecholamines and cyclic AMP act, in the control of aqueous humor outflow. Understanding these processes will help clarify the basis for several types of glaucoma and may help improve treatment or even lead to the prevention of some forms of glaucoma.
- Perform metabolic studies and cyclic AMP and steroid receptor determinations on the tissues that lie between the anterior chamber and Schlemm's canal not only to understand how these may be altered in disease and be affected by hormones and drugs which regulate outflow, but to learn whether these tissues may be involved in the turnover of mucopolysaccharides that may govern resistance to aqueous outflow.

Uveo-Scleral Functional Relationships

- Establish the clinical significance of uveo-scleral relationships and particularly explain how detachment of the choroid and ciliary body may reduce aqueous humor formation, with the aim of potentially applying this knowledge to the development of new forms of treatment for both hypotony and glaucoma. A good animal model would be highly desirable.

Circadian Variation of Intraocular Pressure

- Establish whether circadian variation in intraocular pressure is attributable to variation of aqueous formation or of resistance to outflow. It will then be essential to investigate further whether this variation is in response to hormonal, neural, hypothalamic, or other influences, with the ultimate goal of applying this knowledge to the development of better means of pressure regulation.
- Develop a noninvasive device for continuously monitoring intraocular pressure in glaucoma patients.

Resource Requirements

In the subprogram *Hydrodynamics of the Eye* there are in FY 1977 approximately 48 research grants receiving an estimated total of $3,187,000 in funding from the NEI. To this amount the Panel recommends adding 15 research grants and two research contracts bringing total funding in this category to an estimated FY 1978 level of $4,541,000. Details and a list of recommended projects are contained in the tables at the end of this report.

4

Medical and Surgical Treatment of Glaucoma

MEDICAL TREATMENT OF the glaucomas continues to rely principally on well-established miotics, epinephrine, and carbonic anhydrase inhibitors for the primary glaucomas and on corticosteroids for glaucomas secondary to uveitis.

For certain types of glaucoma, specific forms of surgical treatment are widely preferred over medical treatment, but these account for only a small fraction of all glaucoma cases. Adults who have primary angle-closure glaucoma and infants who have congenital glaucoma are most commonly treated surgically. Iridectomy is performed for angle-closure glaucoma, and goniotomy or trabeculotomy for congenital glaucoma. Such operations in these particular conditions are in most cases curative and without great risk.

In most other types of glaucoma, the most widespread practice is to reserve surgical treatment for situations in which medical treatment has been tried but proved inadequate, as evidenced by persistence of excessive intraocular pressure and progression of optic nerve and vision changes or for situations in which drug treatment has proved intolerable to the patient because of side effects. The fundamental reason that surgery is the second choice in these cases is that its ratio of potential benefit to potential adverse effect is not as good as that for medical treatment.

There are two main objectives in research on surgical treatment of glaucoma: to improve its success rate and to reduce the complications. It is interesting and noteworthy that most innovations in surgical treatment and attempts to reduce surgical complications during the past century have been made by practicing clinicians, rather than by professional research investigators. But, a number of problems remain unsolved. Fundamental research is required if these problems are to be resolved, and it is highly important that they are because the vision of many patients hinges upon the results.

Some innovations that have been made in the surgical treatment of glaucoma have had such obvious value that rigorous clinical comparisons have not been made. Where the advantages are less obvious, there should be controlled clinical trials.

Similarly, there is need to evaluate new medical treatments. Pilot studies of new medications should be made, analogous to the preliminary assessment of a new surgical procedure. Then, if the treatment shows sufficient promise, more formal controlled clinical trials should be planned.

The 1975 report of the National Advisory Eye Council encourages well-designed studies that involve patients with confirmed and suspected glaucoma and that would improve understanding of glaucoma and the ability to manage and, in the long run, prevent it. The Council advised that controlled, randomized clinical trials of medical and surgical therapy should be conducted.

The following observations should be considered in planning future studies:

- Drug studies in animals are applicable only to the species used and under the dosage regimens followed. They serve mainly as a clue to what to look for in man.
- Further single-dose response studies on new drugs in animals should be pursued primarily to indicate possibilities for definitive work in primates and in normal and glaucomatous human patients.
- The mechanisms of action and dose-response relationships during chronic administration of drugs in normal and glaucomatous humans should be studied intensively. Tachyphylaxis, augmentation of response, synergism, and competition between drugs during chronic administration require systematic investigation.[273]

Accomplishments

Research on medical and surgical treatment of glaucoma has brought valuable advances. The discovery, testing, and clinical introduction of carbonic anhydrase inhibitor drugs, such as acetazolamide and methazolamide, have undoubtedly saved the vision of a great number of glaucoma patients, while sparing them from having to undergo surgery. Clinical testing and development of systemic osmotic agents, along with the carbonic anhydrase inhibitors, has helped many patients with acute glaucoma, preparing them better for necessary surgery.

Malignant glaucoma, for which there was previously no known effective therapy, almost inevitably caused blindness. Now, medical treatment provides relief in about half the cases of this disease because of research that tested and demonstrated the effectiveness of cycloplegic drugs, with and without carbonic anhydrase inhibitors and osmotic agents. The remaining cases can now be relieved and probably cured by newly devised surgery based on pars plana aspiration of posterior vitreous and deepening of the anterior chamber.

Testing and demonstrating the effectiveness of anti-inflammatory corticosteroid drugs in the eye has significantly improved the treatment of various forms of uveitis and associated secondary glaucomas. The corticosteroids have also been found valuable in reducing tissue reactions to antiglaucoma surgery, thereby raising the success rate.

Yet, despite these and other accomplishments in improving the medical and surgical treatment of glaucoma, serious needs exist for further fundamental advances in controlling glaucoma and preventing blindness through research.

Research Objectives

- Make the medical treatment of the open-angle glaucomas more effective and reduce the unpleasant side effects
- Reduce the risks and raise the success of surgery for glaucoma
- Establish greater specificity and logical design in selecting treatment for the angle-closure glaucomas

- Improve the treatment of glaucomas secondary to other abnormalities of the eye, especially uveitis
- Devise means to prevent neovascular glaucoma by treating conditions that cause it, and develop more effective treatment for neovascular glaucoma
- Discover means to increase the resistance of the optic nerve head to intraocular pressure

Research Needs and Approaches

Treatment of Open-Angle Glaucoma

The majority of patients with primary open-angle glaucoma, that is not excessively severe and that has been diagnosed before it has caused much damage to the optic nerve head, respond to standard pilocarpine and epinephrine eyedrops. These drugs can reduce the intraocular pressure to a safe level, though the treatment may cause inconvenience because of the need to apply drops several times a day and because of the intermittent dimming and blurring of eyesight it causes.

New drug delivery systems, principally for pilocarpine, have provided means for exposing the patient's eye to a less varied concentration of medication than do ordinary eyedrops, and with a lower peak level.[274–277] Particularly for young people with active accommodation, this has provided greater convenience and less annoyance from intermittent accommodative spasm. However, it has not so far improved the treatment of glaucoma in patients whose pressures cannot be adequately controlled despite frequent application of standard pilocarpine eyedrops. A similar reduction in annoyance from spasm of accommodation, but not necessarily improvement in control compared to the effect of standard pilocarpine eyedrops, appears to have been accomplished by the introduction of aceclidine eyedrops, commonly employed in conjunction with epinephrine.[278–280] This drug has become widely used in Europe but has not yet been approved for noninvestigative use in the United States.

Miotic eyedrops that are stronger than pilocarpine, acting through inhibition of cholinesterase, carry with them the risk of gradually inducing cataracts.[281,282] This has been documented clinically, and recently in monkeys that had their irises removed surgically.[283] However, in facing such severe open-angle glaucoma that it cannot be adequately controlled by the direct-acting miotic eyedrops, such as pilocarpine, in combination with epinephrine and carbonic anhydrase inhibitors, some ophthalmologists and their patients prefer to take the risk of cataract and use the stronger cholinesterase-inhibiting eyedrops rather than turn to antiglaucoma surgery. Cataracts can be removed surgically with a higher degree of success and lower risk than is entailed in antiglaucoma surgery.[2,284] If the glaucoma can be controlled by the most potent medications prior to cataract extraction, there is strong expectation that it can be controlled at least as readily after removal of cataracts.

Other ophthalmologists and their patients prefer, rather than risk development of cataract from strong cholinesterase-inhibiting miotics, to turn to antiglaucoma surgery. This, too, can prove successful and can rid the patient of the need for further medical treatment. However, antiglaucoma filtration surgery does have its own problems and complications, among which is the induction of cataract in older people, though this is not common in young adults.

Because of the unpleasantness of using miotics that cause pupillary constriction and spasm of accommodation for near vision, the risk of induction of

cataract by the strongest miotics, and the fact that in some patients glaucoma is so severe that it cannot be controlled by even the strongest standard medications that the patient can tolerate, the search continues for new antiglaucoma medications. Drugs are sought that may either be more tolerable, more effective, carry less risk of adverse effects on the lens, or possess a combination of all these hoped-for virtues. Among the drugs investigated in the last few years that seem to offer some of these advantages are the beta-adrenergic blocking agents, which can be used as eyedrops. Efforts have also been made to enhance the effectiveness of epinephrine and norepinephrine by employing drugs that increase the responsiveness of the eye to adrenergic stimulation.[285-288] Clinical reports suggest that the beta-blockers may have the greater promise, but this has yet to be established by extensive clinical use.[289,290]

For many years, it has been supposed that the central nervous system may exert some influence on intraocular pressure. Experimental findings and clinical observations relating to this question have occasionally been reported, both pro and con.[291] Recent reports of changes in intraocular pressure after optic nerve section, and also in association with stimulation of portions of the central nervous system, have strengthened this concept.[292–298] These observations and occasional reports of reduction of intraocular pressure by barbiturates, general anesthetics, and cannabis derivatives indicate a need for further clinical evaluation of the effects of psychotropic and other centrally-acting drugs in open-angle glaucoma.[292,299-304] Evaluation and analysis may be complicated, as in the cases of cannabis derivatives and clonidin, by the need not only to take into account the local effects of these drugs on the eye but to assess their indirect effects through the central nervous system as well.[215,305]

Improvements in filtration surgery for glaucoma in recent years consist mainly of techniques for early tamponading of the filtration fistula. This limits an initial excessively free drainage of aqueous humor from the eye, thereby avoiding hypotony and subsequent detachment of the choroid and flattening of the anterior chamber. Consequently, this reduces the risk that peripheral anterior synechias will develop or that a good filtration bleb will fail to form. This has been accomplished by means of the so-called trabeculectomy ab externo or by trephining under a partial-thickness scleral flap. Both of these techniques limit the early, excessively easy drainage of aqueous humor from the eye by means of a flap of sclera covering the fistula from the anterior chamber.[306-310] Both procedures have become popular, but a long follow-up period will be necessary for adequate comparison with older classical filtration surgery, that is, comparing the degree to which intraocular pressure is lowered, the duration of this effect, the susceptibility to infection, and the tendency to induce cataract.

Another but less widely evaluated means for tamponading the filtration bleb consists of fastening a plastic shell to the anterior segment of the eye by means of sutures and by a pressure dressing until a suitable amount of healing takes place in the conjunctival and episcleral tissues. In the hands of its developers, this procedure has appeared quite promising.[311]

In many patients who have both cataract and glaucoma at the same time, each severe enough to need surgery, a considerable number of operations have been performed combining cataract extraction and the filtration operation, or combining cataract extraction and cyclodialysis.[312-319] Experience so far suggests that the latter combination may entail less risk, yet offer reasonable opportunity to control the glaucoma.

Treatment of open-angle glaucoma by laser puncture of the filtration portion of the trabecular meshwork has received much publicity in recent years, and claims have been made of at least short-lived effectiveness.[320-328] A thoroughly documented, controlled clinical evaluation would be welcome.

Intensive laser treatment of the trabecular meshwork in monkeys has been shown to produce chronic glaucoma.[329] This offers a potentially valuable new primate glaucoma model but also gives a warning of need for caution in clinical laser trabeculopuncture.

Treatment of Angle-Closure Glaucoma

In most cases, medical treatment of primary angle-closure glaucoma is aimed at reducing the intraocular pressure in preparation for surgery. Iridectomy is then performed to allow the aqueous humor to flow from posterior to anterior chamber more easily than through the pupil, where the iris is apposed to the lens. Relieving the excess pressure behind the iris in this manner permits the iris to settle back away from the trabecular meshwork and lets the aqueous humor regain its normal access to the aqueous outflow system. This cures the glaucoma; however, if the iris fails to settle back because it adheres to the trabecular meshwork through formation of synechias, or if some other mechanism continues to hold the iris against the trabecular meshwork, glaucoma will persist approximately in proportion to the extent the trabecular meshwork is obstructed. In such cases, other forms of treatment are required.

If the iris is held forward and the angle is kept closed by synechias to such degree that medical treatment cannot be expected to maintain an adequately low intraocular pressure after iridectomy has been performed, it is logical to perform filtering surgery instead of simple iridectomy.[330,331] The extent of peripheral anterior synechias can in some cases be determined preoperatively by gonioscopy with special purposeful indentation of the cornea.[332] Alternatively, the extent of the synechias can be ascertained during surgery, but before iridectomy, by intraoperative gonioscopy. This consists of paracentesis to drain the aqueous humor from both anterior and posterior chambers and injection of saline solution into the anterior chamber which causes the anterior chamber to deepen and the angle to widen, thereby displaying to gonioscopic inspection any synechias that may be present.[330] This method seems to have greatly reduced the problem of determining the extent of peripheral anterior synechias and choosing between iridectomy and filtration surgery. Other problems and their management deserve more attention, but further clinical evaluation of the reliability of the anterior chamber deepening procedure and diagnostic gonioscopy should be carried out in centers with large numbers of glaucoma patients.

The following problems in the management of angle-closure glaucoma are particularly noteworthy:

- Preliminary medical treatment does not always suitably prepare the eye for surgery
- It is rarely possible to know prior to surgery which eyes may have one of the very rare complications in which something other than peripheral synechias holds the iris forward, obstructing the trabecular meshwork, despite iridectomy

In medical treatment prior to surgery of an eye with angle-closure glaucoma, there are several possibilities that need to be compared. Most commonly, the eye is treated intensively with pilocarpine eyedrops, while a carbonic anhydrase inhibitor and an osmotic agent are given systemically. However, the intensive use of pilocarpine is a holdover from earlier days when the other agents had not come into use. In some cases, pilocarpine may cause an adverse shallowing of the anterior chamber rather than provide the desired help in opening the chamber angle.[46-52] With the availability of carbonic anhydrase inhibitors and osmotic

agents to reduce pressure, it may be safer to limit the amount of pilocarpine employed.

It must be ascertained whether using miotics at lower than customary concentrations and doses (in conjunction with standard systemic treatment) in the initial treatment of angle-closure glaucoma would be advantageous. A preliminary report suggests this to be the case.[333] To test this possibility a clinical trial is required in which random cases in an adequate series receive either mild or intensive pilocarpine treatment. Or, the trial could be designed so that the mild pilocarpine treatment is applied first and if after a predetermined time it is judged insufficient the more intensive pilocarpine treatment would be instituted. In either trial the standard systemic medications would be administered to all patients.

In the treatment of angle-closure glaucoma, laser iridotomy presents both potential advantages and difficulties but in selected cases appears to have succeeded.[334,335] Similarly, preliminary information on the use of laser radiation to cause the iris to shrink and become flattened peripherally, so-called laserogonioplasty, in the treatment of angle-closure glaucoma indicates that this method may have special applications.[336] It may possibly offer a special advantage in treatment of nanophthalmos,[41] but more investigation and experience will be needed before the proper use for laser treatment in angle-closure glaucoma becomes clearly defined.

Treatment of the second eye has to be taken into consideration when angle-closure glaucoma has developed and been treated in one eye, because in most cases the second eye also has an abnormally narrow angle that is threatened with closing. It has therefore become common practice to perform iridectomy prophylactically in the second eye. Several clinical investigations have shown this to be an effective and reasonably safe procedure.[44,337-341] Clinical comparisons have also shown that in second eyes that have been treated with miotic eyedrops instead of with prophylactic iridectomy, there has been high incidence of angle-closure glaucoma despite miotic treatment.[338-340]

The value of prophylactic iridectomy in second eyes seems to have been adequately established, but there are opportunities for further clinical investigation in this area.[44] As new methods are developed that may be even safer than iridectomy for management of abnormally narrow angles, there will be need for evaluating their efficacy in prophylactic treatment of second eyes. This should be considered for various means of laser treatment, as well as for possible prophylactic use of the drug aceclidine, which produces miosis but has less of the unwanted effect of pilocarpine on the ciliary muscle and the shape of the lens.[278-280] Similarly, thymoxamine eyedrops, which produce miosis by alpha-adrenergic blockage and do not contract the ciliary muscle, should be further evaluated clinically in comparison with pilocarpine, not only in preoperative treatment of angle-closure glaucoma but also as a potential prophylactic for the second eye.[342-344]

Treatment of Glaucoma Secondary to Uveitis

In treatment of glaucoma secondary to uveitis, it has been disappointing so far that noncorticosteroid, anti-inflammatory agents have seemed considerably less effective in suppressing inflammation in the eyes of human beings than in the eyes of rabbits. Therefore, principal reliance continues to be placed on the corticosteroids, despite their potential adverse effects on intraocular pressure, their risk of inducing cataracts, and their unwanted systemic effects when administered systemically.

Treatment of Neovascular Glaucoma

Neovascular glaucoma has long been a serious problem, occurring as a complication of the occlusion of central retinal vessels and as an increasingly frequent complication of diabetic retinopathy. Now initial comparison of the incidence of neovascular glaucoma in eyes treated by pan-retinal photocoagulation compared with untreated contralateral eyes indicates not only that treatment was clearly beneficial in preserving vision but has reduced the incidence of neovascular glaucoma.[105,106] This opens the door to investigating the effectiveness of photocoagulation in patients who have occlusion of the central retinal vessels and offers hope that the incidence of neovascular glaucoma can be reduced in that condition as well.[345]

Besides this new hope for reducing the incidence of neovascular glaucoma in patients with diabetic retinopathy or with occlusion of central retinal vessels, there is now additional cause for optimism. Observations that extend over more than three years strongly indicate that it is possible by anterior laser treatment to arrest the development of neovascular glaucoma at an early stage when new vessels are first seen in the anterior chamber angle and before extensive peripheral anterior synechias develop.[107] This is accomplished by coagulating the new vessels where they cross the ciliary band and scleral spur, avoiding exposure of the trabecular meshwork itself to the laser beam. This new treatment, performed at a sufficiently early stage before the intraocular pressure has gone up and before extensive peripheral anterior synechias have formed, appears highly promising and appears to be attended by very low risk.

This is an important development that has taken place in only the last few years. Neovascular glaucoma as a rule has led to blindness and in many cases produces severe pain. Previous treatments generally were palliative, aiming primarily at reducing pain. If pain was unremitting, treatment consisted of removal of the eye. Standard antiglaucoma medication and surgery were generally effective only in reducing pain and rarely in preserving vision. Therefore, wider evaluation of these new forms of treatment is clearly indicated.

There is a pressing need to determine whether combined laser treatment of anterior segment new vessels and pan-retinal photocoagulation may significantly improve the results of standard filtering operations in patients who already have developed neovascular glaucoma.

Also, there is need to determine whether laser coagulation of new vessels in the angle and on the iris may improve the safety of removing cataracts from the eyes of patients who also have diabetic retinopathy to improve vision and to permit treatment of the retina by photocoagulation, which is not feasible when a cataract is present. Otherwise, extraction of cataract in patients with diabetic retinopathy appears to hasten the development of glaucoma due to neovascularization in the anterior segment. It is important for the benefit of those patients who now or will in the future have the combined problems of diabetic retinopathy and cataract to evaluate by further careful clinical trials the effectiveness of preparatory laser treatment of vessels in the iris and angle.

Surgical Treatment Problems

Research on glaucoma surgery should be directed toward overcoming the following complications and problems:

Wound Healing in Filtration Surgery

Priority should be given to the support of further basic research on the factors involved in wound healing, especially in relation to function and failure of filtration blebs. In certain individuals, especially young people, and worst in children, there is a tendency for intended filtration blebs to seal over the scleral fistula and to fail to drain aqueous humor and relieve the glaucoma. This is the crucial reason for treatment failure and blindness in some of the most desperate cases of childhood glaucoma. Repeated operations on the same eye tend to end the same way.

Some surgical filtration procedures fail as though caused by a specific characteristic of a given patient, whereas other patients react in an entirely different manner. There may be differences in the composition of the aqueous humor of these different individuals, or some intrinsic difference in their conjunctival and episcleral tissues. There is real need to explain and solve this problem. This may require very basic study of wound healing, involving a number of different scientific disciplines. Such a study proposed by investigators with good ideas and a thorough knowledge of the problem is much needed. Besides experiments with subhuman primates, study of the healing characteristics of other types of wounds in humans (such as those associated with strabismus and cataract operations) could prove valuable.[346, 347]

Cataract Formation as a Complication of Surgery

When deciding whether to perform filtration surgery for glaucoma in older people one of the deterrents nearly always taken into account is the likelihood of speeding the development of cataract.[2,348-350] However, there is practically no research underway to find out why glaucoma surgery may increase the risk of cataract. Yet, an advance in this area could change the treatment of glaucoma considerably. Admittedly, this is a difficult problem to investigate, but new research in this area would be valuable if an ingenious and feasible approach can be proposed.

Among the more obvious factors to be considered and determined is whether a subnormal rate of aqueous humor formation, such as is associated with detachment of the choroid and ciliary body, predisposes to cataract formation. Some surgeons have an impression that if the anterior chamber remains formed and there is no choroidal separation, the incidence of late postoperative cataract is less. An extensive long-term clinical study with a well-designed protocol will be required to determine whether this is correct.

Treatments for the Optic Nerve

Most treatment for glaucoma, either medical or surgical, is intended to reduce the intraocular pressure because this has long been known to be beneficial in slowing or completely stopping changes in the optic nerve or vision. However, other treatments have been proposed and tried from time to time with the aim of benefitting the optic nerve, irrespective of the pressure.[351-354] Most recently, phenytoin (diphenylhydantoin) has been proposed and studied as a potential protector of the optic nerve in glaucoma.[355] If a large, controlled clinical study clearly demonstrates the hoped-for clinical benefits from this medication, it will provide an impetus for further research, possibly on related compounds of lower

toxicity, as well as on unrelated substances which might be shown in animal experiments to protect the optic nerves from the effects of oxygen deficiency.

Priorities and Recommendations

Primary Open-Angle Glaucoma

- Investigate adrenergic drugs that may substitute for epinephrine and beta-adrenergic blocking agents that may reduce the intraocular pressure without disturbing the pupil or accommodation. These compounds should be compared with present standard medications in trials with glaucoma patients, including those who have various degrees of responsiveness to the standard medications.
- Study further drugs that act on the central nervous system to learn whether they affect the pressure and hydrodynamics of the eyes of glaucoma patients.
- Conduct clinical trials and evaluate long-term results of laser treatment of the trabecular meshwork and ciliary band in the angle of the anterior chamber to appraise their place in treating open-angle glaucoma.
- Develop in animals and test in humans treatments which may protect the optic nerve and preserve the visual field in glaucoma in spite of continued elevation of intraocular pressure.

Primary Angle-Closure Glaucoma

- Compare results of initially treating angle-closure glaucoma with low concentrations of pilocarpine to those of intensively applying high concentrations of pilocarpine, in both cases in addition to standard systemic treatment with carbonic anhydrase inhibitors and hyperosmotic agents.
- Conduct clinical investigations in eyes subject to angle-closure glaucoma to determine in which types of eyes treatment with miotic eyedrops acts favorably, causing opening and widening of the angle, and in which types of eyes the same miotic eyedrops act unfavorably, aggravating the shallowing of the anterior chamber and closing the angle. The ultimate aim of these investigations is understanding these differences and differentiating these types of eyes prior to choosing treatment.

Glaucoma Secondary to Uveitis

- Conduct further clinical trials of nonsteroid anti-inflammatory agents in treating glaucoma secondary to various types of uveitis. Correlate results with findings from examining samples of aqueous for evidence of prostaglandins, other mediators of inflammation, and special types of cells.

Neovascular Glaucoma

- Appraise the value of laser coagulation of new-formed vessels that cross the scleral spur in the anterior chamber in the treatment and prevention of neovascular glaucoma, and the value of photocoagulation of the fundus in the prevention of neovascular glaucoma secondary to diabetic retinopathy and occlusion of central retinal vessels, following the lead of preliminary studies.

Surgical Treatment Problems

- Conduct experimental and clinical research aimed at improving the results of filtration surgery in children and young people, and also in certain older people who have an extraordinary tendency to scar down their blebs.
- Carry out experimental and clinical research to clarify the basis for cataract formation after glaucoma operations, with the aim of developing means to reduce the incidence of this common and important complication.
- Perform further clinical trials in patients who have both cataract and open-angle glaucoma to establish the relative advantages and disadvantages for controlling glaucoma and restoring vision of ordinary cataract extraction compared with combined cataract extraction and cyclodialysis or a filtering procedure.

Resource Requirements

NEI funding of *Medical and Surgical Treatment of Glaucoma* in FY 1977 is approximately $458,000 for two specialized clinical research centers. To this total the Panel recommends adding 13 research grants and one contract bringing the total estimated funding for this subprogram to $1,540,000 in FY 1978. The tables at the end of this report provide further details.

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Project and Resource Tables

Table 1: Glaucoma
Total Resource Requirements by Mechanism FY 1978

(Dollars in thousands)

	Research Grants		Specialized Clinical Research Centers		Contracts		Core Centers		Research Career Awards		Research Training		Total
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	Amt.
Estimated Support FY 1977	83	$5,421	2	$ 458	1	$ 91	4	$833	3	$ 85	32	$804	$ 7,692
Additional Requirements FY 1978	58	4,410	2	685	4	428	0	74	2	55	12	180	5,832
Estimated Total Support FY 1978	141	$9,831	4	$1,143	5	$519	4	$907	5	$140	44	$984	$13,524

Table 2: Summary of Recommendations by Subprogram

	Estimated Support FY 1977				Additional Requirements FY 1978				Estimated Total Support FY 1978			
	Number of Projects				Number of Projects				Number of Projects			
Subprogram	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)
1. Etiology of Glaucoma												
A. Developmental Glaucoma	3	0	0	$ 200	3	0	0	$ 237	6	0	0	$ 437
B. Primary Open-Angle Glaucoma	10	0	0	664	6	0	0	474	14	0	0	1,138
C. Primary Angle-Closure Glaucoma	3	0	0	200	5	0	0	395	10	0	0	595
D. Secondary Glaucoma	5	0	0	331	12	1	0	1,212	17	1	0	1,543
Subtotal	21	0	0	1,395	26	1	0	2,318	47	1	0	3,713
2. Optic Nerve and Vision Changes in Glaucoma	14	0	1	930	4	1	1	769	18	1	2	1,699
3. Hydrodynamics of the Eye	48	0	0	3,187	15	0	2	1,354	63	0	2	4,541
4. Treatment of Glaucoma	0	2	0	458	13	0	1	1,082	13	2	1	1,540
Other*				1,722				309				2,031
TOTAL: *Glaucoma*	83	2	1	$7,692	58	2	4	$5,832	141	4	5	$13,524

*Core Centers, Research Career Awards, and Research Training

Note: The three project and resource tables are explained in the introduction to this volume.

Table 3: Recommendations by Subprogram

Chapter 1: Etiology of Glaucoma

Recommendation	Additional Requirements FY 1978: Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Developmental Glaucoma			
1. Elucidate in aniridia the reasons for the changes that take place in the angle as glaucoma develops and evaluate the role of prophylactic surgery (F)	3		
B. Primary Open-Angle Glaucoma			
1. Establish more precisely the relationship of genetic markers in outflow system cells and in lymphocytes to individual differences in the development of various types of glaucoma (F, CR)	2		
2. Determine whether glaucoma affects Blacks or other racial and ethnic groups more frequently, earlier in life, and/or more severely (CR)	2		
3. Identify genetic markers for primary open-angle glaucoma (F, CR)	2		
C. Primary Angle-Closure Glaucoma			
1. Improve methods for diagnostic prediction of angle-closure glaucoma (CR)	3		
2. Determine the manner in which the vitreous body is involved in angle-closure glaucoma and its complications (CR)	2		
D. Secondary Glaucoma			
1. Elucidate more fully the mechanisms which precipitate attacks of secondary angle-closure glaucoma (CR)	2		
2. Establish in human eyes the degree to which prostaglandins are involved in secondary glaucoma (CR)	2		
3. Investigate the fundamental mechanisms of obstruction to aqueous flow in the secondary glaucomas (CR)	2		
4. Clarify the basic mechanism of glaucoma that is associated with the exfoliation syndrome (CR)	2		
5. Establish conclusively the roles of ghost cells, fragmented cells, and macrophages in glaucoma secondary to intraocular hemorrhages (CR)	2		
6. Establish the factors that influence intraocular growth of epithelium and the mechanisms responsible for the associated glaucoma (CR)	2		
7. Correlate iris fluorangiographic studies in neovascular glaucoma with basic research on neovascularization, emphasizing development of an animal model (F, CR)		1 project	
8. Study in animal models the roles of lens proteins, inflammatory cells, and macrophages in lens-induced glaucoma (F)		1 project	
9. Develop more advanced methods for examination of aqueous humor and anterior segment tissue biopsies (CR)		1 project	1
10. Develop better noninvasive methods for diagnosis of lens-induced glaucoma (F, CR)		1 project	
11. Determine the cause of pigmentary glaucoma and pigment dispersion syndrome (F)		2 projects	
TOTAL: *Etiology of Glaucoma*	26	1 (including 6 projects)	0

(Estimated Number of New Principal Investigators Required, FY 1978-80: 22)

Key:
F — Fundamental Research
CR — Clinical Research
CT — Clinical Trial
RD — Resource Development

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
1. Document progression of optic nerve cupping and atrophy by serial stereophotography. Correlate findings with field changes (CR)		1 project	
2. Develop a primate model of chronic glaucoma for correlation of optic nerve head changes with subsequent histopathology; study varied susceptibility to given pressures (RD, F)		1 project	
3. Evaluate the risk to vision from treating systemic hypertension in patients with glaucoma (CT)		1 project	
4. Study predictive value of factors that may indicate varying susceptibility to glaucomatous changes under chronically elevated intraocular pressure (CR)		1 project	1
5. Compare the prevalence and severity of primary open-angle glaucoma among different races and anthropologic types, with special attention to Black populations (CR)		1 project	
6. Compare efficiency of serial stereophotography with photogrammetry and direct ophthalmoscopy for evaluating glaucomatous changes (CT)			1
7. Investigate and document the reversibility of glaucomatous cupping after lowering intraocular pressure (CR)	1		
8. Evaluate whether low-tension glaucoma can be arrested by reducing intraocular pressure through monocular surgery (CT)	2		
9. Identify peculiar or predisposing factors in low-tension glaucoma (CR)	1		
TOTAL: *Optic Nerve and Vision Changes in Glaucoma*	4	1 (including 5 projects)	1

(Estimated Number of New Principal Investigators Required, FY 1978-80:7)

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Formation of Aqueous Humor			
1. Develop better noninvasive means for monitoring aqueous humor formation in monkeys and humans (F, CR)	2		
2. Improve understanding of how carbonic anhydrase inhibitors affect aqueous humor formation (F)	3		
3. Search for substances which increase aqueous humor formation rate for possible use in treating hypotony (F)			1
B. Outflow of Aqueous Humor			
1. Ascertain relative influence of physical factors and metabolic processes on control of aqueous humor outflow (F)	2		
2. Perform metabolic studies and cyclic AMP and steroid receptor determinations on tissues near Schlemm's canal to discover relationship to regulation of aqueous humor outflow (F)	4		
C. Uveo-Scleral Functional Relationships			
1. Establish clinical functional significance of uveo-scleral relationships and explain how choroid and ciliary body detachments reduce aqueous humor formation (CR, F)	2		
D. Circadian Variation of Intraocular Pressure			
1. Determine what factors influence circadian variation in intraocular pressure in glaucoma patients (F)	2		
2. Develop noninvasive device for continuous monitoring intraocular pressure in glaucoma patients (CR)			1
TOTAL: *Hydrodynamics of the Eye*	15	0	2
(Estimated Number of New Principal Investigators Required, FY 1978-80: 14)			

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Primary Open-Angle Glaucoma			
1. Investigate adrenergic agents that may reduce intraocular pressure without disturbing the pupil or accommodation (CT)	1		
2. Investigate central nervous system drugs for effect on intraocular pressure and hydrodynamics of glaucoma patients (CR)	1		
3. Evaluate laser treatment of the trabecular meshwork and ciliary band in the anterior chamber angle (CT)			1
4. Develop treatments which may protect the optic nerve and preserve visual field in spite of continued elevation of intraocular pressure (F)	1		
B. Primary Angle-Closure Glaucoma			
1. Evaluate initial treatment of angle-closure glaucoma with both high and low concentrations of pilocarpine plus standard carbonic anhydrase inhibitor and hyperosmotic agents treatment (CT)	1		
2. Determine in which eyes subject to angle-closure glaucoma, treatment with miotic eyedrops acts favorably or unfavorably (CR)	1		
C. Glaucoma Secondary to Uveitis			
1. Develop clinical trials of nonsteroid anti-inflammatory agents (CT)	1		
D. Neovascular Glaucoma			
1. Appraise value of laser coagulation of new vessels in the anterior chamber and of photocoagulation of the fundus in the prevention and treatment of neovascular glaucoma secondary to diabetic retinopathy and occlusion of central retinal vessels (CR)	2		
E. Surgical Treatment Problems			
1. Wound health in filtration surgery			
a. Improve results of filtration surgery in both young patients and in aged patients who tend to scar down their blebs (CR)	2		
2. Cataract formation as a complication of surgery			
a. Perform experimental and clinical research necessary to clarify basis for formation of cataracts following glaucoma surgery (CR)	2		
b. Compare ordinary cataract extraction with combined cataract extraction and cyclodialysis or filtering procedure for controlling glaucoma and restoring vision in patients with both glaucoma and cataract (CT)	1		
TOTAL: *Medical and Surgical Treatment of Glaucoma*	13	0	1
(Estimated Number of New Principal Investigators Required, FY 1978-80: 11)			

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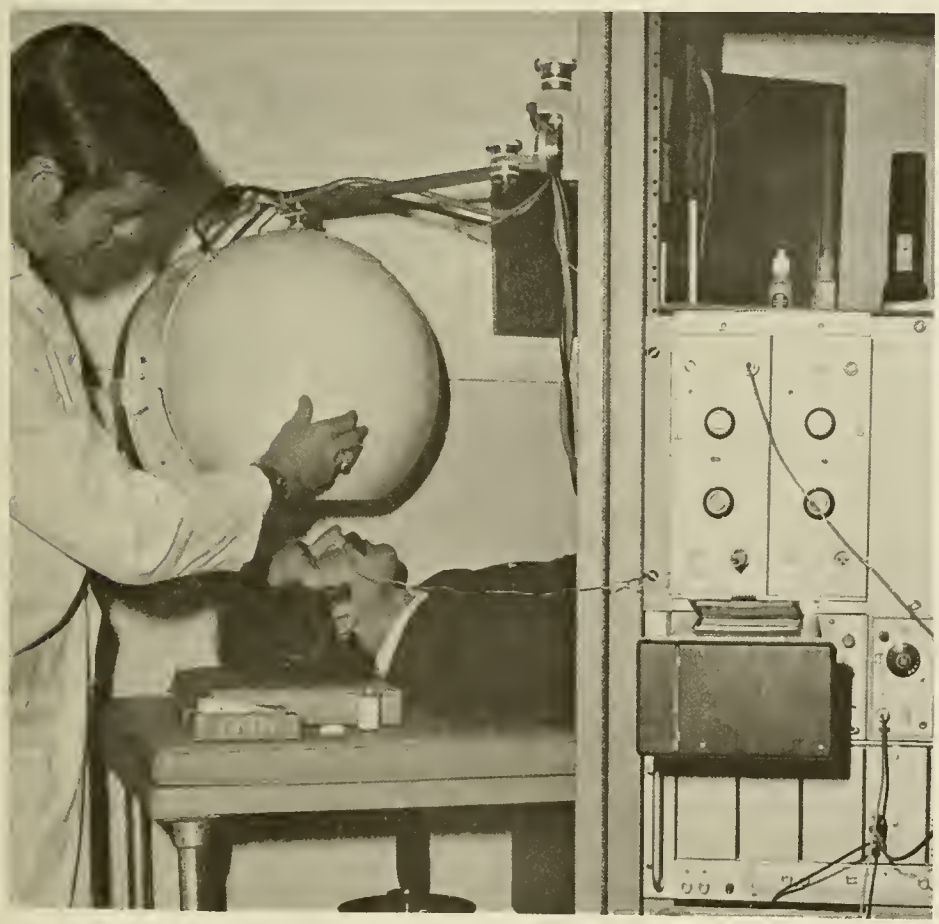
Sensory and Motor Disorders of Vision



Overleaf: *An electroretinogram is made by placing an electrode on the cornea and measuring the electrical response of the retina to light stimulation.*

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Foreword

THE WIDE ARRAY of research activities in the general area of *Sensory and Motor Disorders of Vision* currently being supported by the National Eye Institute and other organizations was reviewed in the first National Advisory Eye Council planning report published in 1975. Because the present Panel believes that the substance and tone of that report are for the most part as pertinent now as they were two years ago, it elected not to cover the same ground but rather to reaffirm the basic concepts articulated in the first report and to focus on a number of selected topics which it believes are of particular significance at this time. As a consequence, although this report includes a summary of the principal conclusions and recommendations presented two years ago, it consists primarily of a discussion of the following specific topics that are judged to warrant special emphasis:

1. Disorders Associated with the Development of the Visual System
2. Strabismus and Amblyopia
3. Disorders Affecting the Control of Eye Movements
4. Potential Applications of Neuropharmacology to Disorders of the Visual System
5. Application of Visual Psychophysical Techniques to the Clinical Diagnosis of Visual Disorders

Together, these cover a substantial proportion of NEI grants in *Sensory and Motor Disorders of Vision*. By selecting these for special consideration, the Panel does not intend to imply that the other areas within this field are less important or less deserving of substantial support.* On the contrary, it wishes to reaffirm the recommendations of the previous reviewing panel; its conclusions remain valid and require no further elaboration.

The five areas selected were chosen for two main reasons. First, they are not only of great significance clinically but are also amenable to experimental analysis. Second, they are currently among the most intensively and critically

*The Panel also wishes to point out that only a few selected references are cited in this report. These references are intended only to indicate the type of work that has been done during the past five years or so on the various subjects considered in the report. On almost every topic an extensive bibliography could have been compiled.

studied areas in the field and, as a result of the work of the past decade or so, hold considerable promise for important new developments and breakthroughs.

It would be appropriate if, in subsequent reviews, the other areas in this program were to be considered in detail. Current support by NEI and other organizations for research in these areas is presented in Volume Three of this report.

The most difficult aspect of this type of review is the attempt to estimate the manpower needs in this field or to determine realistic optima for funding. A single investigator with that rare combination of imagination, technical expertise, and sound judgment that characterizes the most outstanding scientists is likely to contribute more of lasting value than several able but less gifted investigators. Similarly, many important developments have in the past been relatively inexpensive, but inevitably as the problems under study become more difficult and the techniques for their elucidation more sophisticated, the cost of research becomes greater. And when continuing inflation is considered it becomes extremely difficult to provide precise estimates of the need for future funding. There is, accordingly, a substantial subjective element in the Panel's assessments of the need for future manpower and financial resources in this area, discussion of which forms the subject of a separate section in this report.

Introduction

NORMAL VISION DEPENDS upon the coordinated activity of the entire visual system, from the neural and muscular mechanisms which control the direction of gaze at objects of interest to the very highest levels of brain function involved in visual perception and communication. It is appropriate, therefore, that research into the sensory and motor aspects of vision in health and disease should continue to represent a major component of the activities of the National Eye Institute. For the fiscal year 1977, support for all research activities in this area will amount to approximately $10,259,000 or 19 percent of the total research budget of the Institute. Considering the relative importance of the clinical disorders which fall into this general category, the opportunities for effective research in this area, and the quality of the research grant applications which are reviewed each year in this program, the magnitude of this support—both in terms of its actual cost and as a percentage of the overall NEI budget—seems appropriate and readily justified.

In the first report of the National Advisory Eye Council, the entire area of support for research into *Sensory and Motor Disorders of Vision* was reviewed at some length. It is appropriate, therefore, to begin the present report with a brief summary of the major considerations and recommendations of the previous report. This is particularly apposite not only because that report identified the principal subprograms considered here, but also because it dealt with several important topics which have not been elaborated upon in this report. For convenience the previous recommendations will be reviewed under each of the identified five subprograms:

Congenital, Developmental, and Degenerative Abnormalities

The importance of furthering fundamental knowledge of the genetic and environmental factors which collectively shape the development of the visual system was strongly emphasized. Particular reference was made to the continued study of animal models (because most of the analytic methods currently available cannot readily be applied to the human visual system) and to the use of various genetic mutants which affect the visual system in identifiable ways. The important contribution to the understanding of amblyopia by the concurrent studies of experimentally induced strabismus and selective visual deprivation was singled out as one striking example of how fundamental research, initially done for its own sake, may throw light on an age-old clinical problem.

Oculomotor Disorders

In this section particular attention was paid to two important subjects: strabismus and oculomotor control. Both of these subjects are reviewed again in the present report.

Optical and Pupillary Disorders

In view of the high incidence of refractive disorders, these conditions were appropriately dealt with in considerable detail. The need for further work on the etiology of all refractive disorders, and especially myopia, was emphasized, and special attention was drawn to the need for the development of methods to detect a predisposition to "high myopia" and to prevent its progression. While many refractive disorders are adequately taken care of by suitable eyeglasses or contact lenses, there is still room for further improvements in lens design and for research into more satisfactory lens materials, especially for continuous-wear contact and intraocular lenses. It should be noted that these subjects are also discussed in some detail in the reports of the *Retinal and Choroidal Diseases, Corneal Diseases,* and *Cataract* Panels included in this volume.

Visual Sensory and Perceptual Disorders

The first report appropriately drew attention to the impressive advances that have been made in the last two decades in our understanding the way in which visual information is processed from the retina, through various subcortical structures, and within the visual cortex, and in our knowledge of the anatomy of these different components of the visual system. At the same time it was pointed out that much remains to be learned about the normal organization and functioning of the system before such knowledge can be meaningfully applied to the interpretation and ultimately the treatment of disturbed visual function. Four areas deserving further effort were especially highlighted:

- The analysis of the neural transmitters involved at successive levels within the visual system
- The further study of the capacity of the system to reorganize itself after certain types of structural or functional impairment
- The exploitation of certain known psychophysical tests for clinical purposes and the study of other psychophysical parameters
- The perfection of certain noninvasive electrophysiological techniques such as evoked potential recording and ERG's for diagnostic purposes

A number of these topics have been elaborated upon in the present report: their resolution remains as pressing today as when attention was first drawn to them.

Sensory and Motor Disorders Related to Specific Disease Processes

The previous report correctly noted that many disorders affecting both the sensory and the motor functions of the visual system are of a general nature (including, for example, atherosclerosis, tumors, and various inflammatory conditions), the primary etiologies of which lie outside the investigative scope of the NEI. At the same time it was urged that to the degree that these and other

generalized disorders affect the visual system, the NEI should remain open to the possibility of initiating controlled clinical studies and, on occasion, to supporting special scientific investigations bearing upon them.

Rehabilitation

Again, the previous report recognized that rehabilitation service lies beyond the mission of the NEI but, in view of the importance of the subject, urged that continued support be given for fundamental scientific work in this area.

In conclusion, we can do no better than to reprint the summary statement contained in the previous report, together with its special recommendations:

> *Research related to Sensory and Motor Disorders of Vision encompasses a wide range of scientific investigation, disciplines, and research techniques. Particular emphasis is being given to basic study of the development, structure, and function of the visual sensory and oculomotor systems. This emphasis is entirely appropriate at the present state of knowledge.*
>
> *Studies of sensory and motor disorders of vision sponsored by NEI are characterized by especially close association with research sponsored by other Federal agencies and national organizations. Moreover, subprograms in the NEI research activity are closely interrelated. For these reasons, communication among scientists in this broad area of investigation is of major importance.*
>
> *Considered individually, each subprogram incorporates valuable research. In some areas, research is underway that gives promise of yielding clinically useful knowledge in the very near future. The recent finding that use of the eye in the neonate controls the development of good visual function already has led to reevaluation of the treatment of the newborn child with cataract or with strabismus. There is a need to maintain and build on such research, to increase knowledge covering the structure and function of the visual sensory and oculomotor systems, and to apply this knowledge to the prevention, diagnosis, and treatment—including rehabilitation—of visual disorders.*

The following major research needs and opportunities in sensory and motor disorders of vision research were identified by the National Advisory Eye Council in its 1975 report:

- *Further studies of strabismus and amblyopia, especially in primates, should be undertaken and other useful experimental models of these disorders developed.*
- *Physiologic, neurochemical, and pharmacologic studies of oculomotor control, particularly in monkeys, warrant increased emphasis.*
- *There is particular need for research leading to the prevention of degenerative, high myopia and to the prevention of the changes associated with this condition that may endanger sight.*
- *Research on neural mechanisms in the sensory system, and the correlation of these mechanisms with psychophysical function and the processes of vision, should be directed toward maximization of residual visual function following diseases of the visual pathways.*

Importance

In humans, the visual system constitutes the primary source of sensory

information to the central nervous system, and through its interactions with other neural mechanisms, it influences virtually all thoughts and actions.

Disorders or injuries involving any part of the complex and highly integrated visual sensorimotor system can lead to serious lifelong difficulties. These include amblyopia, strabismus, nystagmus, abnormalities of gaze, perceptual dysfunctions, and conditions caused by vascular, infectious, toxic, or metabolic processes which affect the optic nerve, the ocular muscles, and the visual centers of the brain.

Many of these disorders are either congenital or developmental in origin and are therefore influenced by genetic and early environmental factors. Although in some instances their course may be modified or reversed by visual training or surgery, usually their specific cause is unknown, and at present we have no means of preventing or effectively treating them.

The ability to direct and maintain the visual axes in both eyes on a stationary or moving object is one of man's most highly evolved motor skills and makes possible binocular visual perception. Because both sensory and motor elements are involved in this process, defects in either can cause disruption of binocularity and deviation of the eyes.

Strabismus, the clinical designation of the latter condition, affects nearly 1.6 million of the 24 million American school children between the ages of 6 and 11, or nearly 1 child in 14.* Available data shows that each year strabismus necessitates approximately 1.2 million visits to physicians, and an estimated 75,000 hospitalizations are required annually for surgery to correct eye muscle imbalance at a cost exceeding $23 million. A large number of additional cases come to the attention of optometrists and other eye care specialists who employ orthoptics and optical devices in the treatment of this condition.

Although parents are likely to bring a child with either "cross-eye" or "walleye" to a doctor because of their concern about the child's appearance, they usually are unaware of the potential danger of the child's losing vision in the deviated eye. There are nearly half a million annual visits to physicians for such loss of vision, technically known as amblyopia, a condition which usually can be prevented from causing permanent visual damage if it is diagnosed and treated sufficiently early.

The only other visual sensory and motor disorder for which there are reliable statistics is optic nerve atrophy. An estimated 121,000 Americans suffer from uncorrectable visual impairment from this disorder; of these, 41,000 are legally blind. Approximately 103,000 annual visits to physicians are related to optic nerve atrophy, and hospitalization for optic nerve diseases in general totals about 6,000 cases annually.

Accomplishments

In recent years there have been many noteworthy accomplishments in the diverse and complex field of *Sensory and Motor Disorders of Vision*. Because this report concentrates on five selected topics rather than on the entire field of sensorimotor research related to vision, it seemed proper to limit a review of accomplishments to what has been achieved in these areas. This is included under each of the appropriate subprogram headings.

It is worthwhile to note here, however, that aside from the relevance of research in *Sensory and Motor Disorders of Vision* to the improved prevention and

*Except where specifically referenced, incidence, prevalence, and cost statistics quoted in this report can be found in or have been derived from: Westat, Inc, *Summary and Critique of Available Data on the Prevalence and Economic and Social Costs of Visual Disorders and Disabilities*, Rockville, Maryland, 16 February 1976.

management of the many and varied clinical disorders included in this category, investigators in this field have made outstanding contributions to knowledge of the central nervous system, its function, and disorders. For example, the demonstration that visual deprivation at a critical stage in the development of laboratory animals can have a profound effect on subsequent organization and function of the visual system and the development of new methods to investigate such effects have brought research in this field to the forefront of neurobiological investigation. In fact, many of the most renowned and influential neurobiologists are using the visual system as a model for their studies of the structure and function of neural systems. It can confidently be stated that knowledge gained through such efforts is likely to have broad application not only to the solution of visual problems but, because of its relevance to many aspects of central nervous system function and pathology, to a host of neurological and sensory disorders.

Goals of Sensory and Motor Disorders of Vision Research

In developing this report, the Panel was greatly influenced by the fact that many of the principal disorders affecting sensory or motor functions of the visual system are of a general nature (for example, various degenerative, malignant, or vascular disorders) and are by no means unique to this system. The primary etiologies of these disorders are the subject of intense investigation by workers supported by other components of the National Institutes of Health (notably the National Institute of Neurological and Communicative Disorders and Stroke; National Institute of Arthritis, Metabolism, and Digestive Diseases; National Cancer Institute; and National Heart, Lung, and Blood Institute). The National Eye Institute's goals in supporting this research in this area are to:

- Elucidate the normal development, structural organization, and function of the visual system as a basis for better understanding the etiology and pathogenesis of sensory and motor disorders
- Develop improved diagnostic procedures
- Develop methods to prevent and control sensory and motor disorders of vision

Summary of Recommendations

The *Sensory and Motor Disorders of Vision* Panel's specific recommendations for research emphasis in each subprogram are provided in subsequent chapters. The following is a summary of those recommendations:

1. Study embryonic regulation and neural regeneration in the developing mammalian visual system and analyze the mechanisms which lead to the formation of the highly organized visual pathways.
2. Breed animal strains, especially primates and cats, with congenital strabismus and identify morphological and neurophysiological consequences of experimental strabismus in cats and monkeys.
3. Develop a clinical psychophysics to improve diagnosis of strabismic amblyopia, and determine the critical period for its induction and its reversibility through training and drugs.
4. Retrospectively study the effects of surgical and other therapies for strabismus, and establish data banks and registries on the outcome of strabismic surgery.
5. Develop protocols for prospective studies of the efficacy of alternative strabismus therapies.
6. Study muscle mechanics of eye rotation in strabismus, and design eye muscle prostheses based on greater knowledge of eye muscle mechanics.
7. Determine the etiology and pathophysiology of congenital nystagmus and other uncontrolled eye movements, and develop drugs that may be effective in controlling abnormal eye movements.
8. Develop mathematical models of eye movement control and test models of visual brain disease by computer simulation.
9. Compile reliable statistics on the incidence of peripheral and central eye movement disorders.
10. Study relationships between pupillary, accommodative, retinal, and eye movement mechanics.
11. Investigate the genetic, physiological, and behavioral correlates of myopia and evaluate the validity of corrective therapies for refractive errors.

12. Study the neurotransmitters of the retina and central visual system and determine the basis of the selectivity of higher visual neurons and the basis of plasticity in the visual cortex.

13. Develop new tests of visual function capable of detecting incipient disease in rods and cones or visual neural structures and evaluate diagnostic capabilities of existing tests.

14. Investigate binocular (dichoptic) interactions in visual perception and explore abnormal color vision phenomena associated with acute disease and toxic states.

15. Continue application of electrophysiological experiments on humans to diagnose lesions of the retina and visual pathways.

16. Continue visually evoked response (VER) studies during early postnatal development and promote the development of this approach for diagnostic purposes.

17. Develop electrical, mechanical, and optical eye movement technology and perform ERG analysis in clinical populations.

18. Initiate combined single unit and evoked potential studies aimed at understanding the visually evoked cortical potential (VECP) in terms of its neuronal components.

19. Assign a separate program to visual rehabilitation at the National Eye Institute.

20. Promote fundamental research of prosthetic and other mechanisms that may benefit the visually handicapped.

21. Ensure the continued availability of primates to vision researchers.

22. Establish a registry of unusual clinical cases and of interesting animal models to which the scientific community will have access.

23. Apply recent experimental developments in visual psychophysics to the diagnosis of clinically significant visual disorders.

24. Bridge the gap between fundamental laboratory research and the pressing needs in human visual health through the creation of opportunities for collaborative and interactive research and training involving both clinicians and basic scientists.

BASED ON ITS review of all currently supported work in the *Sensory and Motor Disorders of Vision* program, the Panel wishes to make a number of specific policy recommendations for consideration by the National Advisory Eye Council.

Overall Policy Considerations

Visual Rehabilitation

Although at present only two research projects in the area of visual rehabilitation are being supported by the Institute, we believe that this important area merits consideration as a separate program. Its present inclusion within the *Sensory and Motor Disorders of Vision* program probably accounts for its under-representation. The Panel believes that substantial support should be given to fundamental scientific research in this area. We stress the need for fundamental research rather than applied remedial approaches which appear to be reasonably well-supported by other sources.

Primate Animal Models

Because for many types of vision research in the sensorimotor area primates are the most generally useful laboratory animals, the National Eye Institute should make every effort to ensure the continued availability of primates (and especially macaque monkeys) to vision researchers. In assessing research budgets cognizance should be taken of the unprecedented increases in the cost of primates. Macaque monkeys, which as recently as 1972 cost about $80 each, now cost as much as $300, and prices continue to rise as the supply decreases. Comparable increases in the cost of caring for these animals should also be borne in mind.

Clinical and Animal Model Registry

The National Eye Institute should consider the establishment of a registry of unusual clinical cases and of interesting animal models to which the scientific community might have access. Many of those working in the area of visual

psychophysics do not have ready access to clinical material, and at least one potentially important animal model (a population of congenitally strabismic monkeys) seems to have been lost to further study either because the potential usefulness of such animals was not appreciated or because there was no readily available way to maintain them. A registry of unusual albino forms (especially cases with ocular albinism), for example, would be of obvious importance to vision research.

A Nationwide Epidemiological Study of Strabismus

A nationwide program should be established to determine the critical period in human postnatal development when the visual system is most sensitive to the adverse effects of strabismus and partial or complete deprivation. Animal studies make clear that the critical periods vary from species to species (and possibly from one type of deprivation to another). In view of the serious consequences of inadequately treated strabismus or astigmatism (to cite just two examples), it is important that data on the corresponding critical periods in human subjects be gathered as soon as possible. A well-coordinated program involving a number of key centers throughout the country could accumulate this type of data by referring to the clinical histories of strabismic and astigmatic individuals treated at various ages, for differing periods of time, or in different ways. Such a retrospective epidemiological study would require careful planning. We therefore recommend establishing, as soon as possible, a small, carefully selected task force to plan and coordinate this nationwide effort.

Joint Research In Psychophysics

To promote the application of recent experimental developments in visual psychophysics to the diagnosis of clinically significant visual disorders, every effort should be made to encourage joint research efforts between accomplished psychophysicists and clinicians with access to adequate numbers of patients. Although this hitherto neglected area might be adequately supported by research grants, it may be necessary to promote interest in this subject by soliciting joint applications for specific research contracts.

Increased Support For Clinical Research

A majority of Panel members believes that the current manpower distribution and relative levels of National Eye Institute funding reasonably reflect the amount and quality of the work being done in the field of sensory and motor disorders of vision. However, a significant minority favors some degree of redistribution of the Institute's resources to support clinical research on the earlier diagnosis and more effective treatment of such disorders as strabismus. These Panel members believe that in this way, more rapid progress may be made toward one of the National Eye Institute's major goals: to bridge the gap between fundamental laboratory research and the pressing needs in human visual health. Although it is difficult to anticipate how such studies would lead to a better understanding of the cause and long-term consequences of strabismus, it is certainly a matter of some national importance to investigate more carefully the

magnitude of the health care problem which strabismus presents. We know little of the total cost of the long-term management of a single case of strabismus, including expenses for office visits, hospital examinations, surgery, training sessions, and eyeglass changes. Therefore, in order to address the perceived need for better health care in this field, it may be advisable to allocate specifically some portion of the National Eye Institute's research resources to answering these questions—preferably by soliciting appropriate research grants (perhaps for collaboration among several centers around the country) or through research contracts.

Overall Resource Requirements

OF ALL THE tasks facing the Panel, undoubtedly the most difficult is the prediction of future manpower needs. This was clearly recognized by the Panel in its formal meetings and in the individual reports submitted by its members.

All predictions of future needs are, of necessity, based on the existing situation, which is the result not only of deliberate planning but also of a constellation of several unrelated and often fortuitous circumstances. We do not mean to imply by this that the present distribution of manpower and effort is inappropriate; only that it is essential to look closely at the circumstances that gave rise to it. As was pointed out in the Council's previous report, the concentration of research effort in particular areas reflects certain historic trends in what we may term the "sociology of science." Four factors are of special note.

First, given a choice, most serious scientists prefer to work on problems which are likely to yield definitive answers rather than equivocal hypotheses. Science, as Sir Peter Medawar has remarked, is the art of the soluble. As long as this is perceived, scientists will continue to be attracted to soluble problems. Regrettably, by their nature many clinically and socially important issues are not likely to be resolved with the knowledge and techniques currently available.

Second, historically, the most successful developments in science have been those which have had the broadest implications. We need refer here only to the fundamental discoveries which followed the elucidation of the structure of DNA, and the great appeal which molecular genetics in particular, and molecular biology in general, has had for the past two decades. An appreciation of this makes understandable why many of the most able investigators are drawn to such subjects as the functional properties of neurons at different levels in the visual pathway and the regulation of eye movements. The former holds promise of providing for the first time a secure physiological basis for sensory perception in general, whereas the latter provides one of the best models for the general study of motor control.

Third, at any given time, certain topics have an appeal or "glamour" that others lack. The reasons for this type of appeal are often difficult to identify but generally can be traced to one or more significant new technical or observational developments. Thus, whereas comparatively little interest was evoked by earlier experimental studies of visual deprivation, the observation that monocular eyelid closure or experimentally induced strabismus at a critical stage in development could have profound effects on the growth and functional properties of neurons in the lateral geniculate nucleus and visual cortex has made this one of the most

exciting (and, judging from the number of grant applications and awards, one of the most appealing) areas of current interest in vision research. Similarly, the recent introduction of several new neuroanatomical methods has made it possible to investigate a number of fundamental features of the organization of the visual system that were not amenable to study just five or six years ago.

Fourth is the availability of research support and the perception by the scientific community that certain areas are being actively developed or encouraged by various funding agencies. The recent interest of many molecular biologists in cancer research seems directly attributable to this factor, and it seems probable that the increased number of applications for grants for studies of the retinal pigment epithelium may be attributed to the encouragement given to this topic in the previous Council report.

It is in the light of these somewhat intangible elements that all assessments of manpower needs have to be made. Unless a conscious effort is made to influence the direction of work by the assignment of research funds to certain areas, we believe that future trends in sensory and motor research will continue to be shaped by the first three considerations discussed above. But what makes predictions of manpower needs most difficult is that it is virtually impossible to anticipate critical changes in any of these areas. At any time a new technological development may alter the whole aspect of the subject, or a major scientific "breakthrough" might open areas which have either not been open to study or have stirred little previous interest. History has shown that individual scientists will react rapidly to such developments if the necessary funds are available to enable them to do so.

There is general agreement that the present distribution of manpower in the sensory and motor area is appropriate in light of the above considerations. Whatever changes should be made in response to new technological developments or new breakthroughs will undoubtedly occur by the self-correcting mechanisms inherent in the factors that make science appealing. This is certainly true for the basic visual sciences. However, some effort should be made to attract able investigators into four areas of potentially great clinical importance: visual rehabilitation, the retrospective evaluation of the long-term consequences of late or delayed treatment of strabismus and various refractive errors, the development of clinically useful tests based on current psychophysical techniques and knowledge, and efforts to bridge the area between basic research on eye motor control and the application of this research in the clinical setting. As we have pointed out elsewhere in this report, rehabilitation is at present very inadequately represented in program planning. Consideration should be given to placing this important field in a program separate from *Sensory and Motor Disorders of Vision.* Only in this way do we believe that it will receive adequate visibility and attract a larger number of more substantial grant applications.

In view of the important new insights that have come from recent experimental studies of the effects of visual deprivation and experimental strabismus, the time seems opportune to promote a nationwide clinical survey of the effects of inadequate or delayed treatment for such disorders as naturally-occurring strabismus, occlusion of the eye from various causes, uncorrected astigmatism, and other refractive errors. Such a survey (which should draw on the clinical population of several major centers and should perhaps be modeled on the collaborative Diabetic Retinopathy Study) could, by establishing the duration of the critical period for visual deprivation in the human visual system, have important implications for the treatment of these and other congenital disorders of vision. Announcement of such a national survey would undoubtedly attract considerable interest among clinical ophthalmologists and optometrists; we urge the appointment of a small task force of interested clinical investigators to plan and coordinate such a study.

As yet, few of the many techniques that have been developed by psychophysicists for studying the visual system have been adapted for clinical use. Because some of these have potential for great usefulness in the clinic—but are largely unknown to clinicians—some effort should be made to explore this possibility by soliciting applications for joint studies by selected clinicians and basic scientists.

A similar effort should be made to promote the interaction between basic scientists currently working on eye motor control and neurophthalmologists whose responsibility it is to diagnose and treat patients with oculomotor disorders. Consideration should be given to the creation of special fellowships to enable young neurophthalmologists to spend a year or more working in a basic science laboratory, and opportunities should be created for joint research projects involving neurophthalmologists and basic scientists to investigate disordered eye movements in human subjects.

Although the conclusion that these areas may require some redistribution of manpower is relatively straightforward, it is a good deal more difficult to suggest the appropriate number of investigators needed for these or other areas under consideration. Although at present there seems to be an adequate number of investigators working on the anatomy and neurophysiology of the central visual pathways, it is the Panel's feeling that continued support should be given to the training of young investigators in these and in other research areas in order to ensure a steady advance in the acquisition of new knowledge and the preparation of the next generation of teacher/investigators. It is hoped that a significant number of new applications for research in visual rehabilitation will be received during the next several years.

The number of investigators required for the suggested national survey of human visual deprivation will be determined by the number of contributing centers, but could involve as many as 10 to 15 senior investigators for a period of five to seven years. Initially at least, we expect that the number involved in the attempt to apply psychophysical techniques to clinical diagnosis will be quite small—probably no more than three or four groups of clinicians and basic scientists—but depending on the success of the approach, it seems probable that a considerable number of clinical centers will wish to explore this approach.

The reintroduction of training grants in vision research three years ago was an important development, and, if this support mechanism can be maintained, it should ensure the continued entry of able young investigators into the field. We wish to stress that in evaluating such programs three considerations must be borne in mind. First, their importance cannot be realistically assessed except after a substantial period of years. Their ultimate contribution is not to be measured simply in terms of the number of trainees, or the numbers of degrees awarded, or the number of clinical fellows who enter academic ophthalmology or optometry. Rather, these programs should be judged in terms of their total contribution to scientific and clinical progress. It should be realized that one major discovery may affect the vision of thousands, and this more than compensates for the very substantial national investment in the training of clinical and basic investigators.

Second, if there is a prolonged hiatus in the training of the next generation of teacher/investigators, the cost in terms of the inadequate staffing of clinical departments and associated basic science departments may be immeasurable, not to mention the ultimate cost in human suffering.

Finally, there is a serious danger in predicting an excess of "overtrained" people on the basis of current needs or employment opportunities. While there may be a demonstrable excess of personnel in certain areas of science or technology, in the Panel's judgment this is far from being the general case in vision research, and in the area of *Sensory and Motor Disorders of Vision* in particular.

Knowledge of most fundamental processes in this area is still disturbingly inadequate despite the impressive advances made since the establishment of the National Eye Institute.

1

Congenital, Developmental, and Degenerative Abnormalities

THE PANEL CONSIDERS the need for basic research on the development of the central visual system as the highest priority in this field. However, important work remains to be done on the normal development of the human eye, on defects which may occur during its development, and on genetic and acquired abnormalities which may distort the normal pattern of ocular—or retinal—development and lead to impaired vision. The various genetic mutants now available for the analysis of retinal development, especially mice and rats, should be studied further. A whole new area of investigation has been opened up by the discovery that in all albino forms (including human ocular albinism) there are serious visual abnormalities associated with the crossing of an excessive number of nerve fibers at the optic chiasm.[1,2] Research in this area deserves increased support, not only because of its important implications for understanding normal visual development but also for the insights it will undoubtedly provide into the appropriate treatment of individuals suffering from these and related visual defects. As was stated in the Council's previous report:

> [*This work*] *provides a splendid example of how basic genetic or neuroanatomic work, undertaken with no apparent clinical connection, can result in a marked improvement in clinical understanding.*

Disorders Associated With the Development of the Visual System

Any useful understanding of the cause, prevention, and/or correction of congenital defects of the visual system depends upon a much more rigorous understanding of the development of the system than is currently available. For obvious reasons, most knowledge of the development of the human visual system is derived from purely descriptive studies. Although these have been useful in defining certain critical stages in the development of the eye and those central structures to which the retina projects, they are of limited analytic value. They have revealed little or nothing about the morphogenetic mechanisms responsible

for the visual system's normal development or of the probable cause of the more common developmental abnormalities.

Accomplishments

Normal Visual Development

Most analytic knowledge of visual development has been derived from experimental studies done in lower vertebrates—especially teleosts and amphibians.[3-5] Such studies, many of which have been supported by the National Eye Institute, have served to define several key features of visual development. These include:

- The time of origin of neurons in the retina and optic tectum, the homologue of the mammalian superior colliculus
- The time when the ganglion cells of the retina acquire the distinctive properties which determine the precise mapping of their axons upon the optic tectum, and some of the mechanisms by which such "positional information" is acquired and expressed
- The capacity of this system to regenerate an ordered retinotectal projection after interruption of the optic nerve, misrouting of the optic chiasm or optic tracts, or partial ablation of the optic tectum

Although some of the conclusions drawn from these studies are probably generalizable to the visual systems of mammals, including man, many of these findings may not be directly applicable to the mammalian visual system. Regeneration does not occur in the mammalian central visual pathways, and mammals seem to have a limited capacity for embryonic regulation, i.e. the capacity of a surviving part of an organ or tissue to take on the properties of the entire organ or tissue. What little there is probably exists only during the earliest stages of development. To some extent this lack of generalizability has been obviated by the use of avian embryos, which in many aspects of their development closely resemble mammals and have the added advantage of being readily accessible for experimental manipulation.

Developmental Abnormalities

Closely related to the study of the normal development of the visual system is the analysis of the effects of various abnormalities in the system. This has become a matter of considerable interest in recent years following the first dramatic demonstration of the effects of visual deprivation on the growth of cells in the lateral geniculate nucleus.

Research Objectives

- Determine the sequence in which the various components of the visual sensory and motor system develop
- Apply new techniques for tracing neural pathways to the study of the normal and pathological development of the visual system

- Analyze how early visual deprivation and genetic abnormalities affect the development of the neural connections
- Apply this knowledge to the prevention and possible treatment of congenital, developmental, and degenerative disorders of the visual system

Research Needs and Approaches

To date, the National Eye Institute has supported this work broadly and generously. It is evident, however, that much remains to be done and that these subjects are likely to have an increasing appeal to investigators. In the Panel's judgment, this is one of the expanding areas of vision research. Potentially, it is of considerable importance for providing insights into how the visual system normally develops, and it is of practical significance in understanding human visual abnormalities. For these reasons it deserves additional support.

Normal Visual Development

Several technical developments in the last two years now make possible more direct study of the development of the mammalian visual system in general, and the primate visual system in particular. Chief among these are:

- *Thymidine autoradiography,* which can be used to determine the time of origin of neurons in the retina and in such central visual structures as the lateral geniculate nucleus and striate cortex. Interest in this stems from the finding that the final positions that neurons come to occupy and the pattern of connections they establish are determined at, or shortly after, the withdrawal of the cells from the mitotic cycle. The recent application of this technique to the development of the monkey visual system, though extremely costly because of the large amounts of radioisotope needed to label proliferating neurons in the fetuses of pregnant monkeys, has amply demonstrated the importance and usefulness of this approach. There is every reason to believe that the results of these studies are directly applicable to man.
- Improved techniques for *studying mammalian fetuses in utero.* Until comparatively recently, most experimental manipulation of the developing visual system in mammals was limited to the postnatal period. But within the past two or three years a number of studies have been done in utero which have convincingly shown that it is now possible to carry out certain types of experimental analyses in mammalian fetuses that have hitherto only been technically feasible in lower vertebrates. The earliest work of this kind has involved mainly rats and similar small mammals,[6] but a recent report indicates that comparable studies have been initiated in primates.[7]
- Improved techniques for *tracing neural pathways.*[8,9] These include:
  - Retrograde labeling of neurons with protein markers such as horseradish peroxidase
  - Anterograde tracing of pathways in autoradiographs following the administration of radioactive protein or glycoprotein precursors
  - Selective identification of transmitter-specific pathways based either on induced fluorescence, the binding of labeled antibodies to transmitter-

synthesizing enzymes, or the selective uptake of isotopically labeled transmitter substances or their precursors

- Intracellular filling of physiologically identified cells with fluorescent dyes or opaque salts

- Enhanced uptake of tritium-labeled 2-deoxyglucose by areas showing spontaneous or evoked increases in neuronal activity and the relative absence of such labeling after visual deprivation

To a large extent these new methods (most of which have been developed only within the past five years) have replaced more traditional experimental techniques based on the production of various pathological changes. Several examples of their use for studies of visual system development could be cited, but it may suffice to mention the elegant demonstration of alternating bands or stripes within the visual cortex related to one or the other eye, and the dramatic effects of early visual deprivation upon the organization of these so-called "eye-dominance columns."[10] These studies have taken advantage of an important observation that some fraction or component of the labeled materials transported down the optic nerve [following the injection of a tritium (^3H) labeled amino acid or (^3H) fucose] is taken up by the cells in the lateral geniculate nucleus and transported to the visual cortex to visualize directly the cortical distribution of the primary inputs from the two eyes.

- Recent developments in the *biochemistry and molecular biology of cell surfaces.* These have made possible the development of fairly selective procedures for assaying cell-to-cell interactions among the neurons from different parts of the developing visual system (e.g. retina and optic tectum). These approaches offer considerable promise for helping solve one of the central problems in neural development, namely how the axons of one population of neurons "find their way" to their appropriate projection sites and there make contact with the appropriate class of cells.

Priorities and Recommendations

- Study embryonic regulation and neural regeneration in the developing mammalian visual system, and analyze the mechanisms which lead to the formation of the highly organized visual pathways using new techniques such as:
  - Thymidine autoradiography to determine the time of origin of nerve cells at various levels
  - Anterograde and retrograde axonal transport to trace growth of nerve fibers in the visual pathways
  - Electrophysiological studies of the formation, maintenance, and plasticity of visual connections
  - Identification of neurotransmitters specific to these pathways
  - Biochemical studies of neuronal surfaces and the characterization of genetic abnormalities
  - In utero surgery on mammalian fetuses

Resource Requirements

The requirements necessary to carry out these recommendations are provided in the tables at the end of this Panel report. Estimated FY 1977 NEI funding for research in the subprogram *Congenital, Developmental, and Degenerative Abnormalities* will amount to $2,272,000 in support of approximately 35 research grants. The Panel recommends an additional 11 research grants for FY 1978 at an increase in funding of $861,000. This will bring the total for this subprogram to approximately $3,133,000 for that year.

2

Strabismus and Other Oculomotor Disorders

BECAUSE OF THE very considerable progress that has been made in understanding how the normal position of the eye is maintained and how the conjugate movement of the two eyes is initiated and carried out, and because of important new developments in the understanding of anatomical and physiological consequences of strabismus, these two subjects were chosen for special consideration. Despite the impressive progress that has been made, much remains to be done in both these areas to increase understanding of the etiology of strabismus or disturbed eye movements which are such a common concomitant of many neurological disorders.

Strabismus and Amblyopia

Strabismus affects approximately 5 percent of the population. If uncorrected, it may cause loss of vision, double vision, loss of the ability to use the two eyes together, and depth perception by stereopsis may be impaired or absent. Moreover, because of the cosmetic aspects of strabismus, people with this condition often develop emotional problems. Another serious consequence of uncorrected strabismus is amblyopia, which occurs in approximately 2 percent of the population. Other causes of amblyopia, including deprivation of form vision during infancy by congenital cataracts, corneal opacities, ptosis, uncorrected high refractive errors, or a difference between the refractive errors of the two eyes (anisometropia), are also of the greatest importance but are not specifically dealt with in this report. However, they are discussed in other Panel reports in this volume.

Accomplishments

In the past, the clinical aspects of strabismus and amblyopia have been studied by direct observation and by the application of psychophysical and electrophysiological methods. However, this work has added much to knowledge without revealing the nature of the basic disturbance within the visual system. Extension of knowledge of these common afflictions has been impeded by the lack of suitable animal models for research. This situation has been remedied by recent

developments in electrophysiological technique which have made it possible to record directly from single neurons in various parts of the visual system and, subsequently, to study their morphology in considerable detail.

These techniques have recently been applied to cats and monkeys in which strabismus and amblyopia had been produced experimentally.[11-13] Behavioral studies in these animals have revealed that the characteristics of experimental strabismus and ensuing amblyopia are similar to corresponding conditions seen in clinical studies in humans. With the availability of these animal models, a promising beginning has been made toward identifying the neurophysiological and morphological consequences of abnormal visual experience early in life.

It has been shown, for instance, that strabismus, strabismic amblyopia, and stimulus deprivation amblyopia cause marked morphological changes in the cells of the lateral geniculate nucleus and severe functional disturbances in the activity of neurons in the visual cortex, and that these disturbances can be quantitatively correlated with behavioral changes. Moreover, it has been demonstrated that these anomalies occur only during a certain period of susceptibility to abnormal visual experience which ranges in cats and monkeys from birth to approximately the first three or four months of life. During this period the visual system is extraordinarily sensitive to abnormal input; unilateral eyelid closure for as little as a few days may be sufficient to cause permanent functional and morphological anomalies.

Research Objectives

- Determine the optimal time at which ocular surgery should be performed in a child in order to avoid the damaging effects of early visual deprivation
- Identify the time at which, and under what circumstances, a child is most susceptible to strabismus and amblyopia
- Determine the potential for reversing strabismus and amblyopia
- Clarify the pathophysiologic aspects of strabismic amblyopia
- Determine the effectiveness of various forms of treatment for strabismus

Research Needs and Approaches

Research in this field has enhanced understanding of the pathophysiology of amblyopia in humans, has emphasized the danger of uncontrolled unilateral eyelid closure in infants, and has stressed the necessity of removing congenital cataracts or other obstacles to normal retinal stimulation early in life.[14-16] The important question of the optimal time at which ocular surgery should be performed in a child, a current subject of debate among clinicians, may be answered by the careful analysis of further experiments of this kind and by the retrospective analysis of the long-term consequences of various types of treatment initiated at different ages in humans. Further analysis of the structural changes that occur in the visual system as a result of impaired sensory input, and the imaginative application of new insights being gained from neuropharmacology, may eventually lead to entirely new therapeutic approaches.

Because far reaching and health-related implications are likely to evolve from these studies, the need for much additional work clearly exists. It is necessary to

determine the reversibility of functional and structural impairments of the visual system in strabismic and amblyopic animals and to define the nature of the structural changes in the lateral geniculate body and visual cortex by more sophisticated methods.

The present shortage and enormously increased costs of monkeys for research imposes a threat to the energetic continuation of such studies. There is a great need for increased domestic primate breeding programs to satisfy the requirements of vision research laboratories in this country. Because there may well be a pathophysiologic difference between congenital strabismus as it occurs in humans and that produced experimentally in newborn rhesus monkeys, the search must continue for even more appropriate animal models. Congenital strabismus in subhuman primates is exceedingly rare but does occur sporadically. A survey of all primate centers by qualified examiners might identify animals with congenital esotropia, and special efforts should be made to breed a strain of strabismic monkeys for experimental studies of congenital strabismus.

It must be emphasized that the recent developments in strabismus and ambloypia research in animal models by no means supplant the need for continued behavioral, psychophysical, and electrophysiological studies of strabismus and amblyopia in humans. For instance, the age of susceptibility to the effects of strabismus, the minimal period of visual deprivation which may result in amblyopia, and the effects of other forms of abnormal visual experience in humans (such as those caused by anisometropia, unilateral or bilateral surgical aphakia, congenital or traumatic cataracts, corneal opacities, or bandaging of one or both eyes) need to be better defined.[15] Indeed, such knowledge is essential before the optimal age for optical or surgical therapy of these conditions can be determined. Because the clinical data that can be collected by a single investigator are insufficient for developing definitive guidelines, they must be pooled from the entire ophthalmological community by a central agency.

Further studies of suppression characteristics in patients with alternating strabismus, in which first one and then the other eye is preferentially used, may help to clarify some pathophysiologic aspects of strabismic amblyopia. The objective determination of visual functions in strabismic patients by pattern-evoked cortical responses has emerged as a powerful investigative tool in the clinical laboratory, and further progress can be expected using this technique. Clearly, the important questions that need to be explored in animal models will originate in the clinical laboratory, and further progress in this important field of ophthalmic research will be enhanced by close interaction between research-oriented clinicians and basic scientists.

Priorities and Recommendations

- Identify and analyze morphological and neurophysiological consequences of experimental strabismus in cats and monkeys
- Determine the critical period for the induction of strabismic amblyopia in children
- Study reversibility of amblyopic abnormalities via training, drugs, or other therapeutic means
- Breed animal strains (especially primates and cats) with congenital strabismus and related abnormalities
- Develop a clinical psychophysics to improve diagnosis of strabismic amblyopia

- Retrospectively study the effects of surgical and other therapies for strabismus and establish data banks and registries on the outcome of strabismus surgery
- Develop protocols for prospective studies of the efficacy of alternative strabismus therapies
- Study muscle mechanics and eye rotation in strabismus

In addition, the highest possible priority should be given to increasing the number of competently trained investigators to work on strabismus and its consequences and to promote a nationwide epidemiological survey of the long-term consequences of various forms of treatment that have been used, with special reference to the time at which the treatment was initiated.

Disorders Affecting The Control of Eye Movements

Disorders affecting voluntary eye movements, and the occurrence of involuntary movements of one or both eyes in many central and peripheral visual dysfunctions, are among the most serious problems facing the neurophthalmologist. In most cases their etiology is difficult to identify, and even when this is possible the pathophysiology underlying the disordered eye movements is either unknown or poorly understood. At the same time, nystagmus, which is a relatively common concomitant of certain retinal and brain disorders, presents an extremely serious problem for the patient.

Although peripheral oculomotor physiology is fairly well understood and its disorders can be treated by surgery and possibly other means, the situation is much less clear with regard to the central oculomotor system. Yet, central disorders can be extremely disabling because both eyes are usually affected. There seem to be few statistics on the relative frequency with which peripheral and central oculomotor disorders occur. Among the latter, those which are accompanied by various types of spontaneous, uncontrollable eye movements, such as congenital nystagmus, are among the most crippling since they not only seriously interfere with vision but usually prevent the normal development of the visual system. Understanding of the cerebellar and brain stem organization of the oculomotor system is still far from complete, and treatment of eye movement disorders is severely limited by the inability to manipulate pathways in the central nervous system, even if the nature and location of the primary disorder were known.

Accomplishments

Fortunately, considerable progress has recently been made in understanding both the peripheral and central mechanisms which control eye movements. Advances have been rapid and promise not only continued progress but also that this new basic knowledge may soon be applied to disorders of the human oculomotor system.[18–20]

Advances in peripheral oculomotor physiology include a fairly complete quantitative understanding of the force that human extraocular muscles apply to the globe in response to neural commands during normal eye movements. This knowledge has already permitted a more accurate interpretation of several kinds

of abnormal eye movements created by neuromuscular pathology. New information on the different types of muscle fibers has provided clinicians with valuable insights into the role of these fibers in the regulation of eye movements and their implications for pathology. Our quantitative knowledge of muscle mechanics is now so well developed that it is reasonable to predict that sophisticated eye muscle prostheses will be designed in the foreseeable future.

Progress has also been made in understanding how the six extraocular muscles of each eye cooperate with each other to hold the eye in any position of gaze. Quantitation of their forces has led to a new, analytical way to describe and diagnose strabismus and may, in fact, be able to assist in predicting the outcome of corrective surgery. These advances overlap with those described above which are directly concerned with the needs for further basic research and clinical applications in strabismus.

Great strides have been made recently in understanding natural eye movement control from recordings in the oculomotor pathways in alert, behaving monkeys. A flood of new information is available on the neural events that occur in the superior colliculus, cerebellum, vestibular system, and reticular formation. As a result, a number of fairly specific and testable hypotheses can now be advanced concerning the way in which signals flow between these structures and how this information is processed to produce appropriate eye movements. With current techniques, the investigator can place an electrode anywhere in the oculomotor system of an alert primate and observe its natural behavior. Thus, for the first time, long before strategies of posture and locomotion can be worked out in the spinal cord, the oculomotor physiologist has the opportunity of seeing the broad outlines of a complete sensorimotor control system emerge.

The clinical implications of this work are already beginning to appear, and it is now becoming possible to predict the eye movement abnormalities that are likely to occur after lesions that disrupt the circuits at various points. Conversely, the quantitative analysis of eye movements can now be used diagnostically to pinpoint the location of specific lesions. For example, the cerebellum is rapidly emerging as an important structure in eye motor control. From knowledge gained by experiments in animals, disorders of its various parts are now known to cause saccadic dysmetria, gaze nystagmus, loss of pursuit movements, and vestibulo-ocular dysmetria. Equally exciting is the focusing of attention on how the brain may compensate for such cerebellar defects. Thus, when a neurological disorder creates dysmetria in motor control, the olivo-cerebellar system appears to be instrumental both in detecting and repairing the dysmetria. This is of great potential clinical importance in the interpretations of olivary and cerebellar diseases.

From a more quantitative point of view, it is now possible to explain the time course of abnormal eye movements created by muscle palsies, lesions of a major central pathway called the medial longitudinal fasciculus, and lesions in parts of the pontine reticular formation. These analytical explanations, based on neuroanatomically established circuits, will not only aid the clinician by explaining eye movement patterns that have hitherto been totally mysterious but also serve to emphasize the need for new oculomotor tests which will provide more reliable information for diagnostic purposes. For example, measuring the so-called "gain" of the vestibulo-ocular reflex and the ability of patients to suppress this reflex are two new diagnostic tests, the importance of which was only made apparent by the application of systems analysis to these issues.

Basic research is also benefiting from the use of control systems analysis in the oculomotor system. Increasingly, it is becoming possible to direct research into very specific goal-directed channels. In less well understood branches of motor physiology, experimental questions are often vague and qualitative and the results difficult to interpret. Because so much is already known about oculomotor

circuits, and in a form that permits mathematical analysis, experiments can now be designed that aim at specific questions and which yield results that provide specific answers. As in any field, progress begets progress, and in understanding the oculomotor system progress is at present limited only by the availability of research funds. Physiologists in this area need no major breakthroughs to proceed; they can think of more worthwhile projects to do than the available manpower can undertake.

Research Objectives

- Improve understanding of extraocular muscle structure and function in relation to eye movement control in primates
- Collect and analyze biopsy and autopsy material from patients with clinically documented oculomotor abnormalities
- Identify suitable animal models for the analysis of central and peripheral eye movement disorders
- Apply analytical principles of engineering to the study of eye movement control
- Apply basic biomedical knowledge to the diagnosis and treatment of human peripheral eye movement disorders

Research Needs and Approaches

Many questions remain to be answered concerning peripheral eye muscle control mechanisms, such as why the extraocular muscles contain multiply innervated fibers, and what is the nature of the signal generated by muscle spindles during natural eye movements. Knowledge in this area has advanced to the point where future progress will probably be made only through basic research aimed at very specific unresolved functional problems or by applied research which utilizes recent advances to diagnose and repair human peripheral eye movement disorders.

At present, the most promising means of correcting central defects of eye motor control seems to be selective use of drugs, perhaps to potentiate or inhibit specific synaptic neurotransmitter action. Research on this subject is of great importance (see section on Potential Applications of Neuropharmacology to Disorders of the Visual System). Even in the absence of effective means of controlling central oculomotor circuits, great potential benefit can still be obtained by working out the normal operation and neuroanatomy of the eye movement control system, since this will form a foundation of knowledge indispensable to the future treatment of human oculomotor disorders. For this purpose, experimental colonies of primates are absolutely necessary. Work in subprimates, such as cats and rabbits, is still valuable, but it is clear that there are important differences between the control of eye movements in these animals and in primates. And furthermore, because it is not immediately apparent that what is found to be true in a subhuman primate necessarily applies also in man, it is of the greatest importance that the results of these various experimental approaches be closely examined in the light of well-documented clinical observations. Moreover, it is clear that because certain types of disorders (e.g. oscillopsia and various agnosias) can only be identified in human beings, there is a continuing need for clinical neurophthalmological studies in this area.

One important problem that will seriously affect the rate of progress in this field is the inadequate training of most bioscientists in mathematical analysis of complex systems. As yet, this does not seem to be a problem in other branches of motor physiology because knowledge in those fields is too rudimentary to be amenable to systems analysis. This is no longer true in the field of eye movements; further progress depends upon the ability to incorporate new findings into mathematical models which are growing ever more complicated as they grow increasingly realistic and useful.

The mathematical analysis of complex systems is a branch of engineering science that has grown steadily since the 1930's, and a large formal body of knowledge now exists. The development of the field of biomedical engineering around 1960, generously supported by the National Institute of General Medical Sciences, gave impetus to the growth of oculomotor physiology, and many advances in this field were made by bioengineers or physiologists using the techniques of systems analysis. The field is now at the point where even more systems analysis is needed in physiology to pull together the findings of all laboratories into a unified theory of oculomotor circuitry.

While this problem is slowly being recognized in the training of neuroscientists, many remain unaware of its significance. The problem becomes doubly severe when one considers the use of basic scientific knowledge in the ophthalmology or optometry clinic. Not only does the neurophthalmologist know much less about control systems behavior than does his basic science colleague, but he must also examine the whole patient, in whom all systems interact and in whom lesions inevitably cut across the neurological boundaries of individual subsystems (like the saccadic and pursuit systems) and present a bewildering array of signs and symptoms that baffle the best oculomotor control theorists. By the same token, the basic scientist generally does not have the required diagnostic skill to identify appropriate clinical subjects for investigation nor, unless he is working in close association with neurophthalmologists, does he have access to suitable clinical material.

To deal with this problem the Panel recommends that the National Eye Institute promote the sound application of engineering analytical principles to the study of eye movement control and that scientific conferences, special courses, and research fellowships in this area be promoted to familiarize clinical workers with recent developments in the field and to draw the attention of basic scientists to the problems of greatest clinical relevance. We also recommend the creation of special fellowships designed to enable neurophthalmologists and other vision scientists interested in neurophysiology to obtain additional training in the mathematical techniques of systems theory.

We would like to emphasize the key role that neurophthalmologists are likely to play in bridging the gap between the sophisticated research developments in this field and the pressing needs of the diagnostic clinic. Not only will they be critical in identifying suitable subjects for study but also in encouraging the development and exploitation of appropriate technological applications. Every effort should be made to promote the cooperative interaction of basic scientists interested in the problems of eye motor control and neurophthalmologists who deal, on a day to day basis, with disorders of the oculomotor system.

Without some effort of this kind the problem of using mathematical analysis to understand the oculomotor system in health and disease will become worse, and the gap between the theoretician, the physiologist, and the clinical scientist will progressively widen. Already, attempts at modeling eye movement disorders have necessitated complex computer simulation, and as knowledge expands, these models will become increasingly complex and less easy for the clinician to understand or use without special education. There is often a four- to eight-year

lag in the training of new interdisciplinary scientists before they can contribute significantly to the advances of their field. If with NEI encouragement this lag time could be reduced, this would significantly accelerate progress in a field already in a rapid state of growth.

Priorities and Recommendations

- Determine the etiology and pathophysiology of congenital nystagmus and other uncontrolled eye movements
- Design eye muscle prostheses based on expanded knowledge of eye muscle mechanics
- Develop and test central nervous system drugs that may be effective in controlling abnormal eye movements
- Develop mathematical models of eye movement control and test models of visual brain disease by computer simulation
- Compile reliable statistics on the incidence of peripheral and central eye movement disorders
- Perform other neurophysiological studies of disorders affecting the control of eye movement

Resource Requirements

The fiscal year 1977 funding for investigations in *Strabismus and Other Oculomotor Disorders* will be approximately $1,189,000 to support 16 research grants and one specialized clinical research center grant. For FY 1978 the Panel recommends an additional 13 research grants, three specialized clinical research center grants, and five research contracts. The estimated FY 1978 total funding for this subprogram will be $3,655,000. See the tables at the end of this report for more information.

3

Optical and Pupillary Disorders

OPTICAL AND REFRACTIVE errors are by far the most common eye conditions, and although in the great majority of cases they can be readily treated with appropriate eyeglasses or contact lenses, understanding of their etiology is far from satisfactory (see Chapter 3 of the *Retinal and Choroidal Diseases* Panel report). This is particularly true of so-called malignant myopia, in which the risk of blindness is considerable. Research into the cause and prevention of these and similar disorders must be a high priority for the NEI. We would like to reemphasize the point made in the Council's previous report that the development of appropriate animal models, and especially primates, is likely to yield the most fruitful results. In view of the serious consequences of visual deprivation (see Chapter 2, *Strabismus and Other Oculomotor Disorders)*, every effort must be made to improve the quality of contact lenses for children with such conditions as aphakia and aniridia, who are at the greatest risk. The elucidation of the central neural pathways involved in pupillary control is of considerable importance, and the successful development of pharmacological means for manipulating the relevant neural centers is clearly one of the major challenges in this area. This subject is discussed in the following chapter, *Visual Sensory and Perceptual Disorders.*

Recommendations

Although the Panel has not singled out this subprogram for special attention at this time, it does make the following recommendations for additional research:

- Study relationships between pupillary, accommodative, retinal, and eye movement mechanisms
- Investigate the genetic, physiological, and behavioral correlates of myopia
- Evaluate the validity of corrective therapies for refractive errors

Resource Requirements

Fiscal year 1977 funding for research in *Optical and Pupillary Disorders* will be approximately $193,000 to fund three research grants. The Panel recommends

an additional six research grants for FY 1978, bringing the subprogram total for that year to an estimated $662,000. See the tables at the end of this report for a list of recommendations and their associated funding requirements.

4

Visual Sensory and Perceptual Disorders

AN UNDERSTANDING OF the anatomical, physiological, and biochemical mechanisms involved in normal vision is an essential first step to progress in the prevention, diagnosis, and treatment of all sensory and perceptual disorders. No "direct assault" on specific disorders in this field can substitute for the long-term benefit that is to be derived from fundamental scientific studies.

Neural Mechanisms

The elucidation of some of the fundamental mechanisms involved in the processing of visual information at each neural level from the retinal receptors to the visual "association areas" of the cerebral cortex stands out as one of the most remarkable developments in neural science in the past two decades. That much of this work is now supported by the NEI is both appropriate and gratifying. Unfortunately, it is not yet possible to apply much of this knowledge to such important disorders of visual function as oculomotor dyslexia and the various visual agnosias. At the same time, studies of the structural and functional defects that follow visual deprivation/misalignment of the eyes and undoubtedly underlie the conditions collectively referred to as amblyopia indicate how promising and ultimately important fundamental research of this kind can be. Furthermore, it is evident that research on normal vision continues to attract many of the most able investigators. It is noteworthy that in 1967 the Nobel Prize in Physiology or Medicine was shared by three scientists (Wald, Granit, and Hartline) whose work was in this area.

This field was generally well covered in the Council's previous report, and the Panel believes that the current level of support provided by the NEI for work in this area is barely sufficient; it would be a serious mistake to diminish the strong support that this work has received in the past. Although the Panel concurs with the recommendations made in the previous Council report, we believe that the following area is ready for special emphasis and therefore deserves particular attention in this second report.

Potential Applications of Neuropharmacology to Disorders of the Visual System

One of the major obstacles to the effective treatment of many visual disorders, especially those affecting the central visual pathways, is the fact that, once damaged, central nervous tissue cannot be repaired. In certain lower vertebrates such as fish and many amphibians, central pathways like the optic nerve and tract can regenerate after interruption. Unfortunately, for reasons which still remain obscure, mammals seem to have lost this capacity, and there are as yet no reliable reports of regeneration over any but the shortest distances (measured in microns rather than millimeters). Until this obstacle can be overcome the only prospect for effectively dealing with central nervous system disorders affecting vision will be pharmacological. However, before any rational drug therapy can be developed, a good deal more will have to be learned about the normal transmitters involved in the transmission of information from the retina to the visual areas of the cerebral cortex.

Accomplishments

Despite the very considerable progress that has been made in the past decade in elucidating the anatomical organization of the visual system at every level from the retina to the cerebral cortex, in our knowledge of the properties of individual neurons at many of these levels, and of the functions of certain major visual coordinating systems as a whole, comparatively little is known about visual "pharmacology." A number of promising developments have recently occurred in this area, but as of 1976 the number of grants (both from the NEI and other federal and private organizations) for the study of neural transmitters in the visual system, and of the effects of various drugs upon visual function, is extremely small: indeed, no more than six were identified. Moreover, because some of these deal with the effects of such nonspecific agents as marihuana, alcohol, and mercury poisoning, it is evident that there is a real paucity of fundamental work in this field. Because it is clear that the central nervous visual system is not amenable to other forms of treatment, it is most important to encourage fundamental research on the mode of action of the various neurotransmitters involved at each of the many synaptic levels, from the retina to the various visual integrative centers in the brain. Some of the exciting new possibilities in this area may be briefly summarized.

The identification of inhibitory neurotransmitters and their specific antagonists has recently been used to test the longstanding idea that much of the selectivity shown by visual neurons for specific patterns is brought about by specific inhibitory connections.[21-24] For example, the so-called "hypercomplex cells" found in the visual cortex which respond only to a moving, precisely oriented bar of a specific length can be made to respond to a longer bar, without changing the requirements for its orientation or direction, by antagonizing the effect of the inhibitory transmitter, GABA, with bicuculline, a specific antagonist.

In addition to providing new insights into the "wiring diagrams" for the visual neurons' sophisticated patterns of responsiveness, the use of pharmocological tools to study inhibitory interactions may lead to new insights into phenomena like amblyopia which have clinical relevance. It has already been shown, for

example, that some visual field defects in cats can be eliminated by severing the intertectal commissure, a tract with a predominantly inhibitory effect. Moreover, recent work has shown that the amblyopia which follows monocular deprivation in kittens can be reversed by the inhibitory antagonist, bicuculline.

Research Objectives

- Elucidate the pharmacology of inhibitory interactions during development of the visual sensory system
- Characterize the neurotransmitters employed by the visual nervous system
- Establish whether there is a neuropharmacological basis for the regulation of visual nervous system plasticity
- Determine whether drugs can be used to treat sensory and motor disorders that result from early visual deprivation and other causes of central visual pathway damage

Research Needs and Approaches

Pharmacological studies of inhibitory interactions during development may be particularly fruitful since visual experience during cortical development appears to increase the neurons' selectivity for visual patterns and since selectivity is often brought about by inhibitory mechanisms.

The widespread distribution of the peptide-releasing factors in parts of the brain outside of the hypothalamus suggests that they may have other roles, possibly as transmitters. The development of specific reagents for detecting these peptides now makes worthwhile their investigation in a functionally-defined system like the visual pathway.

The huge body of work on the fluorescent fiber systems discovered by the Swedes is now being applied for the first time to the study of single neurons and to specific pathways in the visual system. Of great interest is the recent work suggesting that the critical period for plasticity in the visual cortex may be dependent upon the catecholamine fiber system. Work of this kind may help to establish a neuropharmacological basis for the regulation of plasticity and is of obvious relevance, therefore, to the important problems of visual rehabilitation. Perhaps the availability of a "plasticizing" agent could enhance the effects of therapy begun after the critical period is over.

Progress towards the development of such therapy will be slow, partly because fundamental knowledge of visual pharmacology is still limited, and partly because the experiments required are extremely difficult. The synaptic transmitters involved in the visual cortex are probably the same as those involved in most other parts of the nervous system, and they are probably involved at more than one kind of synapse within the visual cortex itself. This creates problems in trying to work out the pharmacology of the visual cortex, and therapeutic intervention in this process could lead to problems with side effects that may be insoluble. However, only additional basic studies will determine whether or not there are real possibilities for specific pharmacological treatment.

Even when the basic transmitter mechanisms are known, the not inconsiderable problem must be faced of delivering therapeutic agents, which may act on their release and/or uptake, to the appropriate parts of the visual system. If, as previously indicated, the same transmitters are used in many different neural

systems, the systemic administration of most therapeutic agents may well be excluded. It will require considerable imagination and careful collaboration between clinicians, pharmacologists, and physiologists to overcome these difficulties. As a first step towards this, the Panel proposes that more grants be solicited for research in visual system pharmacology and that at least one specialized research center be established to focus specifically on this issue.

Priorities and Recommendations

- Study the neurotransmitters of the retina and central visual system
- Determine the basis of the selectivity of higher visual neurons
- Determine the basis of plasticity in the visual cortex

Psychophysical Functions

Visual psychophysics has made considerable strides in the past decade, and the time now seems opportune to attempt to apply some of the sophisticated testing procedures that have been developed by psychophysicists to clinical diagnosis. Early in its deliberations the Panel identified this area as one deserving special attention, and some potential applications of visual psychophysics to the diagnosis of visual disorders are considered in the following section.

Application of Visual Psychophysical Techniques to Clinical Diagnosis of Visual Disorders

The investigation of the visual sense by psychophysical procedures continues to be one of the most valuable tools in the armamentarium of the researcher. The important advantage of this approach is that it concentrates uniquely on the human visual apparatus and that its measurements are obtained in the presence of the high level of functional integrity of the nervous system that is associated with consciousness. The major difficulty that accompanies this approach is the possibility of confounding the manifestations of several levels of processing in the nervous system, e.g. retinal, geniculate, striate cortical, association cortex, etc.; however, it should be possible in time to account for this fully and in so doing provide a whole new range of diagnostic tools for the clinical ophthalmologist and optometrist.

Accomplishments

A wide variety of nonintrusive techniques have been developed for the study of normal visual function. These include studies of the adaptation process in the retina which permit differentiation of the roles of different classes of receptors as well as the discrimination of neural and photochemical mechanisms. Where disease processes may selectively influence receptors or the supporting mechanisms of vision, such tests may be extremely useful for early diagnosis.

Perhaps the most significant capability of the visual mechanism is its capacity for spatial resolution. This is commonly measured in terms of visual acuity. However, normal visual function involves many discriminations of contrast and spatial patterns which do not normally approach limits of acuity. These discriminations are believed to depend upon interactions which occur at the level of the retina and more centrally in the visual nervous system. Several tests have been devised to study the various mechanisms believed to underlie these processes. These include studies of the spatial modulation transfer function, the Westheimer effect, and a variety of masking effects. Many of the measuring techniques employed can be used to discriminate retinal from more central mechanisms by dividing the visual stimulus between the two eyes so that interactions can only occur at central points where signals from the two eyes converge. Thus, the use of binocular and monocular presentations may permit the discrimination of the central and peripheral mechanisms.

Tests of the temporal resolution capability of the visual system have been applied for many years in attempts to study variations from the normal and also as an index of more generalized neurological effects. In recent years the development of tests of the temporal modulation transfer function has permitted considerably refined interpretation of temporal resolution studies. In spite of these refinements and increased recognition of the significance of the results of such tests, their application for clinical diagnosis of visual disorders has been extremely limited.

One of the oldest and most well-established examples of the clinical application of psychophysical testing is in the study of color vision. A variety of tests have been developed and several have been well-standardized for clinical application, including pseudo-isochromatic plates, the FM 100 Hue Test, and the Nagel anomaloscope. These tests were designed for and best serve assessment of congenital color defects. There has been very little systematic effort to relate acquired defects in color vision to the disease processes or the toxic effects of a variety of drugs which give rise to them. Variations from normal color vision are a remarkably frequent concomitant of the long-term administration of a variety of drugs, and they appear relatively frequently in association with disease. Yet, they have not been adequately exploited for diagnostic purposes.

Research Objectives

- Determine the feasibility of applying existing visual function tests to the differential diagnosis of retinal and sensorimotor disorders of vision
- In so doing, promote interaction between basic scientists and clinicians in order to hasten the practical application of these techniques in the everyday clinical setting

Research Needs and Approaches

Although visual psychophysics is now widely recognized as a subject of considerable importance in its own right, the Panel wishes to emphasize particularly the potential application of certain psychophysical procedures to the analysis of various visual disorders. And when it comes to the application of psychophysical findings to ocular and visual dysfunction, there is interest in

associating one or another aspect of the subject's response with events occurring in a well-defined structure or region within the eye or visual pathway. In the long run it is hoped that it will be possible, by measuring specific alterations in responses to various psychophysical tests that are readily administrable to patients in a clinical setting, to localize incipient malfunction quite specifically to such structures as the outer segments of the rods or cones, or to particular groups of optic nerve fibers that go, for example, to the pretectum or to the lateral geniculate nucleus.

Before this can be done, research is critically needed to determine whether any of the already known visual function tests can be used for differential diagnosis in retinal and sensorimotor diseases. Such investigations must pay careful attention to test parameters and to the characterization of the disease and its stage of development in the patient. Because of their highly technical character these studies are likely to be best carried out as joint ventures between seasoned clinicians and well-trained psychophysicists.

Although it has long been known that scotopic processes (i.e. those measured in the dark-adapted eye) are very much more sensitive to the effects of reduced oxygen, carbon monoxide, a variety of toxic substances, and various sorts of trauma, this fact is not commonly exploited in ophthalmological diagnosis. In addition to adaptation, the Stiles-Crawford effect, an apparent result of the greater directional sensitivity of the cones than of the rods, permits discrimination of rod and cone function. Neither has this effect been widely exploited for diagnostic purposes.

Psychophysical tests of visual function, which permit discrimination of peripheral from central neural mechanisms, and which may permit discrimination of various mechanisms within the retina, can be used in conjunction with nonintrusive electrophysiological tests such as the electroretinogram and visually evoked cortical potentials. These procedures also permit discrimination of various retinal mechanisms and cortical effects. Their use in clinical diagnosis is increasing, but they are still employed relatively infrequently. The visually evoked cortical potentials are actually more widely used for the diagnosis of neurological disease than for the study of purely visual effects.

Specific tests may be able to predict susceptibility to certain diseases. Given such an indicator, appropriate treatment could be initiated at a much earlier stage of the disease than is now possible. The implication of this for the high-risk patient may be considerable. It is hoped that in time these and other tests of visual function not commonly used clinically, including modulation transfer functions and the Stiles-Crawford effect, will provide valuable information concerning certain ophthalmic diseases.

A major reason for the relatively limited application of psychophysical and electrophysiological procedures in clinical diagnosis is the complexity of the techniques used combined with the current lack of training provided to ophthalmologists and optometrists in these areas. At the same time many basic scientists are unaware of the very substantial possibilities available for the study of disease processes and the effects of toxic substances on vision. Every effort should be made to promote productive interactions between basic visual scientists and clinicians to facilitate progress in this potentially very important field. Special workshops and joint research projects involving basic and clinical investigators may serve this function,* but in addition, special training fellowships should be offered to enable interested clinicians to spend a period of some months learning first hand the essential techniques of psychophysical

*One such workshop sponsored by the NEI was held on September 9 and 10, 1976.

testing. Comparable opportunities should be provided for interested psychophysicists to spend time in a clinical setting learning the special needs of clinical practice.

Although retinal function testing, such as dark adaptation, electroretinograms, and electro-oculograms, has proved to be an invaluable asset in diagnosing hereditary retinal and choroidal diseases, classification of acquired color defects is still relatively unsophisticated. Most clinics use a combination of screening plates, FM 100 Hue Test, and Nagel anomaloscope—tests designed for congenital color defects. There is as yet litle systematic effort to relate an acquired defect to the underlying disease. For example, a blue-yellow defect measured by the FM 100 Hue Test is the most common defect observed and occurs in a wide variety of problems.

The case for developing psychophysical applications in ophthalmology is clear: the careful study of retinal function in early disease states may not only help determine the locus of a particular disease process (e.g. in the pigment epithelium, on the photoreceptors, or at more central levels) but perhaps also permit earlier diagnosis and more prompt treatment.

Priorities and Recommendations

- Evaluate the diagnostic capabilities of existing tests, e.g. acuity, grating sensitivity, and Westheimer function in retinal and cerebral disease
- Develop new tests of visual function capable of detecting incipient disease in rods and cones or visual neural structures
- Investigate binocular (dichoptic) interactions in visual perception
- Explore abnormal color vision phenomena associated with acute disease and toxic states

Electrophysiological Techniques Applicable to Man

Because it is usually not possible with human subjects to use invasive electrophysiological techniques (such as penetrating the eye or the brain with recording electrodes), considerable interest attaches to the development of new methods and the refinement of existing techniques for electrophysiological testing in human subjects. Although it is unlikely that these will ever have the analytic power of the more widely used experimental approaches, a good deal can be learned from surface recordings, especially with the aid of computer averaging procedures. This topic was well reviewed in the previous report, but the following additional observations may be pertinent.

Records from the Human Retina

Records of the human electroretinogram (ERG) have been made for many years by the use of contact lens electrodes placed on the surface of the eyeball. Recently, the usefulness of the human ERG has been greatly improved by

technical progress in signal averaging, noise reduction, and stimulus configurations that isolate the photopic (daylight vision) or scoptic (night vision) responses of the retina.

Another recent development is the isolation of responses from the receptors themselves, as distinct from responses coming from neural cells in the retina. These developments have immediate application to the diagnosis and assessment of retinal dysfunction in the human eye.

Records from the Human Brain

At the level of the visual cortex, records of electrical activity can also be made. Visually evoked responses (VER) can be recorded by the use of standard EEG surface electrodes applied to the scalp over the region of the occipital pole of the brain. The usefulness of this gross method of recording has also been greatly extended in recent years by improved methods of amplification and isolation of the response, the use of multiple arrays of electrodes, and a better understanding of the origins of the responses as revealed by microelectrodes used in experimental studies with animals. Using this approach, evidence can be obtained about the normal or pathological function of certain areas within the visual processing centers of the brain.

Of particular clinical importance are new methods for studying visual function in human infants. Not only is it possible to record ERG's and VER's, but there are also new behavioral measures that depend on observations of the infant's eye movements. The eyes have been carefully observed as they saccade to follow moving targets or to fixate on stationary ones. In this way, the clinician can judge whether or not the infant can detect differential features of pattern and color. It has now become possible to measure visual acuity, color vision, and eye movement control in infants less than six months of age. Using this type of analysis it should be possible to detect such disorders as strabismus and amblyopia at a much earlier stage and to initiate appropriate treatment sooner.

Recommendations

In addition to the priorities listed elsewhere in this report, special attention should be directed towards the following:

- Continue application of electrophysiological experiments on humans to diagnose lesions of the retina and visual pathways and correlate visually evoked response with perceptual functions
- Continue VER studies during early postnatal development and promote the development of this approach for diagnostic purposes
- Develop electrical, mechanical, and optical eye movement technology and perform ERG analysis in clinical populations
- Initiate combined single unit and evoked potential studies aimed at understanding the visually evoked cortical potential (VECP) in terms of its neuronal components

Resource Requirements

In FY 1977 there will be approximately 76 research grants with an estimated total funding of $4,936,000 for research in the subprogram *Visual Sensory and*

Perceptual Disorders. The Panel recommends an additional 27 research grants and two new specialized clinical research center grants, bringing the total FY 1978 funding of research in this subprogram to $7,359,000. See the tables at the end of this report for more information.

5

Sensory and Motor Disorders Related to Specific Disease Processes

AS WAS INDICATED under the statement of program goals, much of the pathology affecting the central visual pathways, such as the various degenerative, neoplastic, or inflammatory disorders, is of a general nature and not specifically related to the visual system. As such, these disorders do not generally come within the province of the National Eye Institute. Many are being actively investigated by other components of the National Institutes of Health, and only when their relationship to the eye or the central nervous system is of paramount importance should their investigation be considered for support by the National Eye Institute.

Resource Requirements

For research in the subprogram *Sensory and Motor Disorders Related to Specific Disease Processes,* estimated FY 1977 funding will be $65,000 to support one research grant. The Panel recommends an additional four research grants in FY 1978 for a funding increase of $313,000. This will bring the total for this subprogram to an estimated $378,000 for FY 1978. See the tables at the end of this report for additional information.

6

Rehabilitation

REHABILITATION OF BOTH the blind and the partially sighted is recognized by the Panel as a subject of considerable importance, although at present the National Eye Institute supports few grants in this area. Because this subject applies to visual disability from all causes, not just sensory and motor disorders, it deserves greater prominence in the overall program of the National Eye Institute. The Panel therefore was unanimous in recommending that the Institute assign a separate program to visual rehabilitation. Every effort should be made to promote the scientific study of prosthetic or other mechanisms that may benefit the visually handicapped. Although much work is being done by many governmental and private agencies and charitable organizations to improve the quality of life and communicative capacity of these individuals, the National Eye Institute is, and should remain, the principal source of support for fundamental scientific work in this important area.

Resource Requirements

The estimated FY 1977 funding for *Rehabilitation* is $128,000 to support two research grants. The Panel recommends an additional three research grants and two research contracts for FY 1978 at an estimated total increase of $539,000. Total funding for that year will amount approximately to $667,000. See the tables at the end of this report for further details.

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Project and Resource Tables

Table 1: Sensory and Motor Disorders of Vision
Total Resource Requirements by Mechanism FY 1978

(Dollars in thousands)

	Research Grants		Specialized Clinical Research Centers		Contracts		Core Centers		Research Career Awards		Research Training		Total
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	Amt.
Estimated Support FY 1977	133	$ 8,633	1	$ 150	0	$ 0	3	$497	7	$173	16	$ 806	$10,259
Additional Requirements FY 1978	64	5,001	5	1,000	7	1,070	1	103	7	192	39	585	7,951
Estimated Total Support FY 1978	197	$13,634	6	$1,150	7	$1,070	4	$600	14	$365	55	$1,391	$18,210

Table 2: Summary of Recommendations by Subprogram

	Estimated Support FY 1977				Additional Requirements FY 1978				Estimated Total Support FY 1978			
	Number of Projects				Number of Projects				Number of Projects			
Subprogram	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)	Research Grants	Specialized Clinical Research Centers	Research Contracts	Amount (in thousands)
1. Congenital, Developmental, and Degenerative Abnormalities	35	0	0	$ 2,272	11	0	0	$ 861	46	0	0	$ 3,133
2. Strabismus and Other Oculomotor Disorders	16	1	0	1,189	13	3	5	2,466	29	4	5	3,655
3. Optical and Pupillary Disorders	3	0	0	193	6	0	0	469	9	0	0	662
4. Visual Sensory and Perceptual Disorders	76	0	0	4,936	27	2	0	2,423	103	2	0	7,359
5. Sensory and Motor Disorders Related to Specific Disease Processes	1	0	0	65	4	0	0	313	5	0	0	378
6. Rehabilitation	2	0	0	128	3	0	2	539	5	0	2	667
Other*				1,476				880				2,356
TOTAL: *Sensory and Motor Disorders of Vision*	133	1	0	$10,259	64	5	7	$7,951	197	6	7	$18,210

*Core Centers, Research Career Awards, and Research Training

Note: The three project and resource tables are explained in the introduction to this volume.

Table 3: Recommendations by Subprogram

Chapter 1: Congenital, Developmental, and Degenerative Abnormalities

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Disorders Associated with the Development of the Visual System			
1. Study embryonic regulation and neural regeneration in the developing mammalian visual system and analyze the mechanisms which lead to the formation of the highly organized visual pathways using new techniques such as: a. Thymidine autoradiography to determine the time of origin of nerve cells at various levels (F) b. Anterograde and retrograde axonal transport to trace growth of nerve fibers in the visual pathways (F) c. Electrophysiological studies of the formation, maintenance, and plasticity of visual connections (F) d. Identification of neurotransmitters specific to these pathways (F) e. Biochemical studies of neuronal surfaces and the characterization of genetic abnormalities (F) f. In utero surgery on mammalian fetuses (F)	11		
TOTAL: *Congenital, Developmental, and Degenerative Abnormalities*	11	0	0
Estimated Number of New Principal Investigators required, FY 1978-80: 16)			

Key:
F — Fundamental Research
CR — Clinical Research
CT — Clinical Trial
RD — Resource Development

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Strabismus and Amblyopia			
1. Identify and analyze the morphological and neurophysiological consequences of experimental strabismus in cats and monkeys (F)	3		
2. Determine the critical period for the induction of strabismic amblyopia in children (CR)	3		
3. Study reversibility of amblyopic abnormalities via training, drugs, etc. (CR)		3 projects	
4. Breed animal strains (especially primates and cats) with congenital strabismus and related abnormalities (RD)		1	2
5. Develop a clinical psychophysics to improve diagnosis of strabismic amblyopia (CR)		3 projects	
6. Retrospectively study the effects of surgical and other therapies for strabismus (CR) and establish data banks and registries on outcome of strabismus surgery (RD)			2
7. Develop protocols for prospective studies of the efficacy of alternative strabismus therapies (CT)		1 project	
8. Study muscle mechanics and eye rotation in strabismus (CR)		2 projects 1	
B. Disorders Affecting the Control of Eye Movements			
1. Determine the etiology and pathophysiology of congenital nystagmus and other uncontrolled eye movements (F, CR)		3 projects	
2. Design eye muscle prostheses based on expanded knowledge of eye muscle mechanics (CR)		1 project 1	
3. Develop and test central nervous system drugs that may be effective in controlling abnormal eye movements (CR, CT)	3		
4. Develop mathematical models of eye movement control and test models of visual brain disease by computer simulation (F, CR)	2		
5. Compile reliable statistics on the incidence of peripheral and central eye movement disorders (RD)			1
6. Perform other neurophysiological studies of disorders affecting the control of eye movement (F, CR)	2		
TOTAL: *Strabismus and Other Oculomotor Disorders*	13	3 (including 13 projects)	5

(Estimated Number of New Principal Investigators Required, FY 1978-80: 68)

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
1. Study relationships between pupillary, accommodative, retinal, and eye movement mechanisms (F)	2		
2. Investigate the genetic, physiological, and behavioral correlates of myopia (F)	2		
3. Evaluate the validity of corrective therapies for refractive errors (CT)	2		
TOTAL: *Optical and Pupillary Disorders*	6	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 14)			

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Neural Mechanisms: Potential Applications of Neuropharmacology to Disorders of the Visual System	5		
1. Study the neurotransmitters of the retina and central visual system (F)	5		
2. Determine the basis of the selectivity of higher visual neurons (F)	5		
3. Determine the basis of plasticity in the visual cortex (F)	5		
B. Psychophysical Functions: Application of Visual Psychophysical Techniques to Clinical Diagnosis of Visual Disorders			
1. Evaluate the diagnostic capabilities of existing tests, e.g. acuity, grating sensitivity, and Westheimer function in retinal and cerebral disease (CR)		4 projects	
2. Develop new tests of visual function capable of detecting incipient disease in rods and cones or visual neural structures (F)		2 projects	1
3. Investigate binocular (dichoptic) interactions in visual perception (F)		2 projects	
4. Explore abnormal color vision phenomena associated with acute disease and toxic states (F, CR)		2 projects	1
C. Electrophysiological Techniques Applicable to Man			
1. Correlate visually evoked response with perceptual functions (F)	1		
2 Continue visually evoked response studies during early postnatal development and promote this approach for diagnostic purposes (CR)	1		
3. Develop electrical, mechanical, and optical eye movement technology and perform electroretinography analysis in clinical populations (CR)	3		
4. Initiate combined single unit and evoked potential studies aimed at understanding the visually evoked cortical potential in terms of its neuronal components (F)	2		
TOTAL: *Visual Sensory and Perceptual Disorders*	27	2 (including 10 projects)	0

(Estimated Number of New Principal Investigators Required, FY 1978-80: 72)

Chapter 5: Sensory and Motor Disorders Related to Specific Disease Processes

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
A. Vascular and Circulatory Abnormalities* (F)	1		
B. Inflammatory Diseases* (F)	1		
C. Metabolic, Toxic, and Traumatic Disorders* (F)	1		
D. Tumors* (F)	1		
TOTAL: *Sensory and Motor Disorders Related to Specific Disease Processes*	4	0	0
(Estimated Number of New Principal Investigators Required, FY 1978-80: 6)			

*For additional information see *Vision Research Program Planning, Volume 1,* report of the National Advisory Eye Council Vision Research Program Planning Committee, DHEW Publication No. (NIH) 75-664.

Chapter 6: Rehabilitation

Recommendation	Additional Requirements FY 1978		
	Research Grants	Specialized Clinical Research Centers	Research Contracts
1. Continue development of optical, electronic, and mechanical visual substitution and aid devices (RD)	2		
2. Evaluate the effectiveness of visual aids in facilitating mobility and education (CR)			2
3. Develop training and educational methods for the visually handicapped (CR)	1		
TOTAL: *Rehabilitation*	3	0	2
Estimated Number of New Principal Investigators Required, FY 1978-80: 16)			

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Vision Research Training

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Introduction

IN THE PERIOD during and shortly following World War II the potential benefits of medical research to the general welfare of society were dramatically demonstrated by such remarkable advances as the development of penicillin for the treatment of infectious diseases, the control of tuberculosis, the discovery of an effective treatment for hypertension, and the eradication of poliomyelitis, a scourge of children and young adults. Federal officials and legislators concluded that the health of the Nation could be improved even further. Consequently, large sums of money were appropriated and distributed through the National Institutes of Health for the purpose of stimulating more intensive biomedical and clinical research.

In 1968 the problems associated with visual disorders were recognized by the Congress to be of sufficient importance to deserve the creation of a specific federal program to conduct and support research in this field. Therefore, the National Eye Institute was established as a component of NIH, and the relative priority of its activities set by a designated appropriation. To accomplish the desired objective of developing knowledge that could be applied to relieving serious vision disorders, it was recognized that funds would have to be expended to train new research personnel and to promote the development of new research groups having the necessary expertise to solve the problems related to blindness and loss of vision. Vision research training, therefore, was undertaken as an essential component of the national research policy to foster improved prevention, diagnosis, and treatment of blinding and disabling eye diseases.

The future of training as part of the national vision research effort must evolve from (a) a consideration of the existing program, including its record, and (b) a review of factors impinging upon or potentially affecting the continued development of the program. The Vision Research Program Committee therefore considered these two items in formulating its recommendations to the National Advisory Eye Council.

1

Current Vision Research Training Programs

THE NATIONAL EYE INSTITUTE has recognized that research productivity depends as much on the quality of investigators and their working environments as on the number of investigators. Therefore, within the limits of legislative and executive authority, it has responded to scientific needs by providing opportunities for training individuals in the research laboratories of established investigators and by promoting the development and maintenance of centers of vision research and training that use multidiscipline approaches in the investigation of serious eye and visual system problems. The current research training authority of the National Eye Institute is derived from Title I of Public Law 93-348, the National Research Act, which was enacted in 1974. This Act authorizes individual postdoctoral research fellowship (F32) and institutional fellowship (T32) awards. The latter may have a predoctoral component.

In the following sections training support will be considered as it is or has been available for the individual and the institution.

Individual Awards

A variety of mechanisms exist for facilitating the advancement of individuals at different levels of research career development. Predoctoral training is supported by the institutional fellowships (T32) which are considered in the following section. By contrast, postdoctoral support is provided not only through the institutional training awards but also through individual fellowship awards (F32) under the National Research Service Awards program. Applications for these individual postdoctoral fellowships are reviewed in national competition, and awards are made to qualified young scientists who seek additional in depth training for a period up to three years following the receipt of a doctoral degree.

Academic Investigator Awards (K07) are designed to help an individual become established as an independent investigator in an academic or comparable research setting. Eligible candidates have the equivalent of three to seven years of postdoctoral training, and awards are limited to three years. The completion of a formal clinical residency meets the requirement for postdoctoral training.

Research Career Development Awards (K04) are granted in small numbers (e.g. five per year) to individuals who have established reputations as highly promising

independent investigators. Each candidiate must be the recipient of an NIH research grant with at least three years of commitment remaining. The award enables recipients to place almost exclusive emphasis on research for five years; this can be an invaluable mid-career opportunity.

National Research Service Awards (F32) were first made in fiscal year 1975. In prior years similar awards were known as Postdoctoral Research Fellowships (F02) except in 1974 when they were known as Weinberger Fellowships (F22). Similarly, prior to 1975 there were the Special Research Fellowships (F03), which met many of the needs that are now fulfilled by Academic Investigator Awards (K07) and, in addition, were more flexible in supporting purely clinical programs. For the purpose of simplifying the review of vision research training these older programs will be consolidated with and considered as part of the current programs under the new titles.

The National Eye Institute, which was authorized by Congress in 1968 and received its first appropriation in fiscal year 1970, has had a record of contributing to the development of new investigators through individual postdoctoral awards. This is documented in the accompanying tables. Table 1 shows the number of awards made and their annual direct costs for the three types of postdoctoral programs from 1970 to 1976. Table 2 shows the aggregate data for the seven years as distributed by sponsoring unit.

The total funds expended for postdoctoral awards have been essentially constant since 1971 (Table 1) with an average allowable direct cost of $1,606,260. Due to the effects of inflation, this represents a gradual but substantial decrease in the level of effective funding. The fluctuations in 1973 and 1974 were due to the impounding of funds by the President and the subsequent release of these monies. Within this relatively constant base it is noteworthy that in the last two years the number of individual fellowships (F02, F22, and F32) and Research Career Development Awards (K04) has tended to increase, while the number of grants of the Academic Investigator Award type (F03 and K07) has decreased. This is significant since the latter award is the preferred postdoctoral fellowship for a clinician who has completed a residency program. Of those that hold medical degrees, 87 percent hold or have held NEI postdoctoral fellowships of the Academic Investigator type. Of the total group granted Academic Investigator type awards, 72 percent had professional doctoral degrees in optometry or medicine rather than Ph.D. degrees, whereas of those having National Research Service Awards only 5 percent had O.D. or M.D. degrees.

Individual National Research Service Awards are directed toward training in research areas encompassed by the five research programs of the National Eye Institute: *Retinal and Choroidal Diseases, Corneal Diseases, Cataract, Glaucoma,* and *Sensory and Motor Disorders of Vision.* Within this framework, research sponsors are widely distributed, with over one-half of the training provided in nonclinical academic departments. Approximately 45 percent of those holding Research Career Development Awards are working in ophthalmology departments (Table 2). Academic Investigator Awards are held by some individuals seeking guided research experience that will be used in a different career setting and by others who are establishing a research base in an institutional setting in which they expect to remain.

The review of applications for individual postdoctoral fellowships and Research Career Development Awards is conducted by Study Sections of the NIH Division of Research Grants and by the National Advisory Eye Council. The review of applications for Academic Investigator Awards and National Research Service Award institutional fellowships is conducted by the National Eye Institute's Vision Research Program Committee and the National Advisory Eye Council. The results seem to be independent of the group responsible for the initial review, as Table 3 demonstrates. About 90 percent of the applications were

Table 1

Individual Research Training Awards and Direct Costs by Type of Award (Fiscal Years 1970-1976)[1]

Fiscal Year	National Research Service Award (F02, F22 & F32)		Academic Investigator Award (F03 & K07)		Research Career Development Award (K04)		Total Direct Costs Allowed
	Number	Cost	Number	Cost	Number	Cost	
1970	17	$ 109,853	23	$ 239,573	19	$ 471,137	$ 820,563
1971	31	292,705	36	563,093	26	722,220	1,578,018
1972	51	347,650	56	871,063	17	371,839	1,590,552
1973	36	230,745	26	388,864	19	462,049	1,081,658
1974	80	1,097,052	21	421,881	21	596,236	2,115,169
1975	72	782,018	12*	234,758	29	645,265	1,662,041
1976**	105	1,368,085	10*	277,131	31	750,604	2,395,820
TOTAL	392	$4,228,108	184	$2,996,363	162	$4,019,350	$11,243,821
Average cost per grant year		$ 10,786		$ 16,285		$ 24,811	

*Represents K07 awards only
**Includes Transition Quarter (15-month period)

Table 2

Individual NEI Postdoctoral Awards by Sponsoring Unit and Type of Award (Totals for Fiscal Years 1970-1976)[1]

Unit	National Research Service Award (F02, F22 & F32)		Academic Investigator Award (F03 & K07)		Research Career Development Award (K04)	
	Number	Percent	Number	Percent	Number	Percent
Hospital Departments	1	—	9	5	8	5
Ophthalmology Departments	76	19	76	41	72	45
Surgery Departments	8	2	6	3	11	7
Other Medical School Departments	95	24	23	13	40	25
Other University Departments	151	39	42	23	29	17
Schools of Optometry	18	5	10	6	2	1
Other	43	11	18	9	—	—
TOTAL	392	100	184	100	162	100

approved by the initial review groups. However, available resources have limited awards to 70 percent of approved applications. Thus, 63 percent of those applying have been successful in obtaining awards.

Four hundred and fifty-nine new awards were made to individuals during the seven-year period 1970-76. These awards were for periods lasting from one to five years (Table 3). Current NEI guidelines for the first two types of awards (F32, K07) suggest a minimum period of two years for each award.

The National Eye Institute offers a *Special Visual Sciences Research Award* program (R23) which is designed to provide research support for newly trained investigators who complete their training no more than five years prior to the beginning date of the proposed project. Although not a training program, the R23 program is intended to support new investigator research career development by offering the newly trained investigator the opportunity to develop new concepts and techniques and to obtain preliminary research results which may be of value in preparing a regular research grant application (R01). Direct costs for the R23 program are currently limited to $10,000 per year for three years, and funds may not be expended for the salary of the principal investigator. The review process for these awards is the same as for regular research grants. A special allotment of funds is not made for this type of grant. A number of "small grant" programs have been successfully established in several other Institutes within NIH.

Institutional Awards

When the National Institute of Neurological Diseases and Blindness was established in 1950, there were only a few groups in the United States that were organized for research in vision. Most vision research was conducted by individuals who were isolated in academic departments that were concerned with a specific research discipline. In most medical schools, ophthalmology was either organized as a division of the department of surgery or was not recognized as an organizational unit. The responsibilities of ophthalmology were covered by volunteer faculty members with a primary commitment to patient care. Similarly, most schools of optometry were not prepared to meet the demand for research. Therefore, institutional grants were used by the National Institute of Neurological Diseases and Blindness to assist in "establishing, expanding, or improving training opportunities."

Graduate Training Grants (T01) related to vision and disorders of the visual system were first awarded in 1954; at the time the National Eye Institute began operation in 1970, 61 were active. An additional 11 grants were awarded in fiscal years 1972 and 1974 by the National Eye Institute so that a total of 72 institutions received some support. After 1977 only 12 grants will be active, and the program will be completely phased out by June 1979.

The Graduate Training Grants were provided (a) to improve the institutional environment in which the proposed research training was conducted, and (b) to enable the institution to pay subsistence stipends and allowances to full-time trainees in order that they could participate in the training program. Indeed, the recipients of these awards generally referred to them as and considered them to be development grants.

These grants may be viewed as the first phase in the process of creating centers for vision research. This phase involves the creation of units or departments with a small core of full-time investigators. In the second phase, these units obtain research project grants as a base for the support of their research, and then in the third phase embark upon more comprehensive training and development of new

Table 3

Action on New Applications for NEI Individual Postdoctoral Support by Type of Award (Totals for Fiscal Years 1970–1976)[1]

Type of Award	Received and Reviewed	Recommended for Approval After Scientific Review	Percent Approved	Approved and Funded	Percent Funded of all Applications Approved
National Research Service Award (F02, F22 & F32)	416	384	92	283	74
Academic Investigator Award (F03 & K07)	249	204	82	141	69
Research Career Development Award (K04)	63	58	92	35	60
TOTAL	728	646	89	459	71

Table 4

Distribution of Graduate Training Grants (T01) by Sponsoring Unit and Grant Years of Support (Totals for Fiscal Years 1954–1976)[1]

Sponsor	Grant Years	Percent of Total
Hospital Departments	53	7
Ophthalmology Departments	471	61
Surgery Departments or Divisions of Ophthalmology	172	23
Other Medical School Departments	27	3
Other University Departments	27	3
Schools of Optometry	5	1
Other	19	2
TOTAL	774	100

Table 5

Status of Ophthalmology in Accredited Medical Schools by Fiscal Year and the Existence of a Graduate Training Grant[2]

	FY 1961-62		FY 1966-67		FY 1971-72		FY 1976-77	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Schools with Training Grants								
Department Status	29	57	34	65	40	74	46	85
No Department Status	22	43	18	35	14	26	8	15
Subtotal	51	100	52	100	54	100	54	100
Schools without Training Grants								
Department Status	23	72	23	70	20	53	29	53
No Department Status	9	28	10	30	18	47	24	47
Subtotal	31	100	33	100	38	100	53	100

investigators in eye research. The record of the Graduate Training Awards and their sequellae must be viewed from this perspective.

The average Graduate Training Grant was in effect for ten years, with the shortest period being four years and the longest 23 years. Forty-four of the awarded grants were in effect for over ten years. The average annual direct cost of a grant was approximately $54,000; an average of 31 percent of this money was assigned to faculty salaries, although there was an enormous variation in the use of awards within different institutions. This was because established institutions were able to use a much larger proportion of the funds to support trainees, while other institutions with small research staffs very appropriately used a larger proportion of the grant money to build a nucleus of full-time faculty that was then available to train and develop new investigators. The distribution of these grants by sponsoring unit is shown in Table 4. Most of this support was used to develop ophthalmology units in medical schools and in hospitals closely affiliated with medical schools.

Departments of ophthalmology formed and developed to a remarkable degree during the period in which Graduate Training Grants have been available. Many recipients of such grants have noted in their progress reports that the receipt of the grant was a major contributing factor in achieving departmental status for the ophthalmology unit.[1] Data from the Association of American Medical Colleges[2] (Table 5) document the growth in the number of departments of ophthalmology during the past 16 years. More specific information comes from the heads of 40 of the 54 ophthalmology units that have been awarded training grants. Eighteen of these units became departments coincident with or subsequent to the receipt of the training grant. During the period of time that the grants were in effect, the average number of full-time faculty increased from two to ten, and the number of research project grants received by these departments increased from an average of less than one to six. These figures are averages and reflect a mixture of units including developed departments and others without any full-time faculty prior to the receipt of a training grant.

Institutional *National Research Service Awards* (T32) are similar to traditional training grants in that the recipient institution is responsible for the selection of predoctoral and/or postdoctoral fellows. Support is available not only for stipends but also for maintaining and upgrading the research environment; however, the amount of the latter type of support is related to the number of trainees and is limited to a fraction of total fellowship support. This program was first supported in fiscal year 1975. Its intent is to encourage work in selected priority disciplines as determined by the National Advisory Eye Council. At present, areas supported by NEI include immunology and genetics, pharmacology, epidemiology, physiology, biochemistry, developmental biology, psychophysics and physiological optics, pathology, and clinical research in vision. Fellowships are limited to individuals who are seeking full-time research training; for those with clinical backgrounds this is usually at a postresidency level. There is a special interest in supporting training programs that will increase the number of clinical investigators who are competent in the methodology of epidemiology and biostatistics.

In the first year of the T32 program, FY 1975, the total costs of awards that were made in the five programs of the National Eye Institute were as follows:[3]

Retinal and Choroidal Diseases	$ 334,039
Corneal Diseases	114,722
Cataract	0
Glaucoma	282,722
Sensory and Motor Disorders of Vision	331,684
TOTAL	$1,063,167

In addition to training grants, the National Eye Institute provides support to established research groups through *Research Center (Core) Grants* (P30) and *Specialized Clinical Research Center Grants* (P50). Core Center Grants support shared resources or facilities that are needed by a group of established investigators. To be eligible for core support a research group must already have several active research project grants from the National Eye Institute. Core awards are made on a competitive basis after review and recommendation by the Vision Research Program Committee and the National Advisory Eye Council. Specialized Clinical Research Center Grants are designed to facilitate application of scientific methods to clinical outpatient research on a specific disease or problem. Awards are made to established units that can demonstrate that they have the necessary competence and facilities to carry out the proposed program. Both of these awards contribute to the quality of the institutional research environment and thus enhance opportunities for excellence in vision research training.

2

Factors Affecting Training Programs

THE NATIONAL RESEARCH ACT of 1974 provided for a national study to be undertaken to establish the qualitative and quantitative needs for biomedical and behavioral research personnel, to assess current research training programs, and to determine modifications that may be required. To meet this legislative requirement, the Department of Health, Education, and Welfare contracted with the National Academy of Sciences to conduct a continuing study. The Academy's initial report was submitted to the Secretary of Health, Education, and Welfare on May 7, 1976.[4] Certain comments and recommendations in the report are pertinent to this review and are quoted in the *Appendix*.

Opportunities for Research

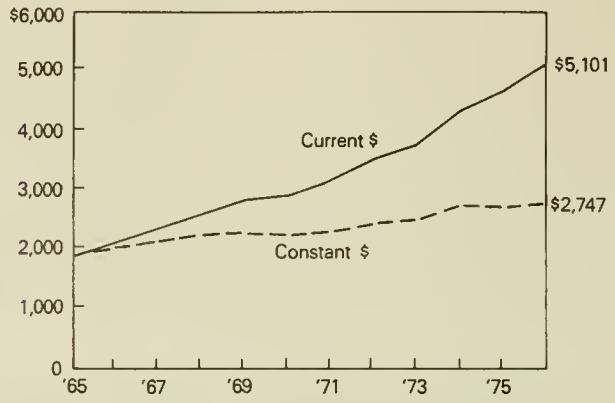
In considering the continued need for training programs, one must consider whether research opportunities or positions will be available for newly trained investigators. This, in turn, depends on available resources.

The estimated support for biomedical research by source in FY 1975 is tabulated in Table 6. In that year the federal government provided 61 percent of the funds for research and development in the field of health.[5] In FY 1975, 96 percent of the support for vision research was federal in origin with 76 percent of the total from the National Eye Institute and an additional 7 percent from other Institutes of NIH. As a result of better reporting of funding sources, FY 1976 support of vision research by the federal government was 97 percent with 70 percent of the total supported by the NEI and an additional 11 percent from other Institutes of NIH.

Over the past ten years biomedical research has dropped from 4.8 percent to 3.9 percent of the total expenditures on health. The absolute expenditure for health research and development, however, has increased from $1.9 billion to $5.1 billion per year. The trend is depicted in the chart on the next page.

There has been a gradual increase in support even in constant 1965 dollars. In vision research, the National Eye Institute expenditures increased from $22.5 million to $43.7 million between FY 1970 and FY 1975. In constant 1965 dollars, this is an increase from $18 million in FY 1970 to $25.3 million in FY 1975. If present trends continue, it is reasonable to expect increases so that resources for

National Support for Health Research and Development 1965-1976
(Dollars in Millions)



Totals are given in current and constant 1965 dollars. The latter are based on the revised biomedical research and development deflator: 1965=100.

research will at least keep pace with inflation. There may, however, be shifts in priority among the various areas of federal health spending.

Institutions of higher education perform about half of the health research and development supported by the federal government. A major portion of the funds is channeled through the National Institutes of Health and in vision research through the National Eye Institute. The distribution is shown in Table 7. In vision research, medical schools and hospitals receive 72 percent of the awards. An additional 20 percent of the awards are made to other units of universities. Thus, the university is the predominant employer of individuals involved in research related to vision and visual disorders.

Research in universities is conducted in part by research professors and research groups that are supported specifically for this purpose. Their numbers are determined by the availability of research dollars. In addition, faculty members who are employed to fill positions that are required principally for education or patient care represent a resource for research. The degree to which such research will be directed toward the field of vision will be influenced by policies that are established for training and for allocating research funds.

University departments outside medical schools are not expected to expand significantly in the immediate future; the opportunities for research in vision will depend on the particular interests of individual faculty members (interests that may have been initiated at the predoctoral level) and on the availability of research support. Vision research opportunities in basic medical science departments will be similar to those in other academic departments.

By contrast, the faculties of health professional schools are likely to expand in coming years as a result of increased demands for physicians and other health care personnel, decreased immigration of foreign medical graduates, and increased university responsibility for graduate and continuing professional education. Clinical research on the visual system will be largely vested in departments of ophthalmology and schools of optometry. Training grants, research project support, faculty practice plans, specialization, and other factors have led to the development of many strong institutional units. As these units increase in number there will be an accompanying increasing need for trained clinical scientists.

Areas Needing More Research

The need for biomedical research training in any given discipline is related to the importance of the disease problem(s) to which it is relevant and the degree to which the results of the training can be applied when required.

The National Eye Institute has categorized vision research into five programs, and a relative rating can be given to each of these in terms of its prevalence as a health problem. Four measures of the problem of visual disability are shown in Table 8. Over 10 million people were estimated to have impaired vision in 1972; the Table, however, is limited to indices that reflect severe disability. The average percent distribution is only significant as a relative figure for comparative purposes. In Table 9, the expenditure for research and research training in each program can be compared with an average of the measures of the problem. The relative support for a program parallels, however, the distribution of grant applications (Table 10) rather than the prevalence of the disorder. This is true in spite of the fact that a higher percentage of research applications in the *Cataract* program are approved and funded. The discrepancy in the *Cataract* program is due to the comparatively small number of applications that have been received.

Table 6

Estimated National Support of All Health Research and Development and Vision Research by Source (FY 1975)[5]
(Dollars in Thousands)

ALL HEALTH RESEARCH AND DEVELOPMENT			VISION RESEARCH		
Source	Dollars	Percent	Source	Dollars	Percent
All Sources	4,610,000	100	All Sources	57,866	100
Federal	2,799,000	61	Federal	55,785	96
NIH	(1,846,000)	(40)	NIH	(48,298)	(83)
NEI	(44,133)	(1)	NEI	(44,133)	(76)
All Other	1,811,000	39	All Other	2,081	4

Table 7

Estimated Percent of Total Funding of NEI Research Grants by Type of Recipient (FY 1975)[5]

Type of Recipient	NIH ($1,146,000,000)	NEI ($30,000,000)
Medical Schools	55	65
Other Units of Higher Education	25	20
Hospitals	9	7
Other Nonprofit Institutions	10	7
Other	1	1
TOTAL	100	100

Table 8

Four Measures of the Problem of Visual Disorders—Percent Distribution by NEI Program[1,7]

NEI Program	Prevalence of Severe Visual Impairment: 1,135,000 cases (1972)	Prevalence of Legal Blindness: 347,000 cases (1972)	Days of Care in Short-Stay Hospitals: 3,201,000 (1972)	Expenditures for Surgery: $273,700,000 (1974)	Extent of the Problem: Average Percent Columns 1-4
Retinal and Choroidal Diseases	47	47	17	9	30
Corneal Diseases	6	7	13	6	8
Cataract	19	18	37	72	37
Glaucoma	18	16	17	3	14
Sensory and Motor Disorders of Vision	10	12	16	10	11
TOTAL	100	100	100	100	100

Table 9

NEI Expenditures for Extramural Research and Training Compared To Extent of The Problem—Percent Distribution by NEI Program (FY 1976)[1]

NEI Program	Research $35,308,000	Extent of the Problem: Average Percent*	Difference	Training $4,592,663	Extent of the Problem: Average Percent*	Difference
Retinal and Choroidal Diseases	36	30	+ 6	24	30	- 6
Corneal Diseases	17	8	+ 9	19	8	+11
Cataract	10	37	-27	10	37	-27
Glaucoma	16	14	+ 2	20	14	+ 6
Sensory and Motor Disorders of Vision	21	11	+10	27	11	+16
TOTAL	100	100	—	100	100	—

*See last column of Table 8

Table 10

Action on Research Grant Applications by NEI Program (FY 1976*)[1]

NEI Program	Received and Reviewed	Percent of Total	Approved and Funded	Percent Funded of All Applications Approved	Percent of Total
Retinal and Choroidal Diseases	130	37	68	62	34
Corneal Diseases	53	15	30	67	15
Cataract	27	8	19	83	9
Glaucoma	31	9	21	91	11
Sensory and Motor Disorders of Vision	108	31	61	63	31
TOTAL	349	100	199	67	100

*Includes Transition Quarter (15-month period)

These figures are relevant to determining future training needs. The high prevalence of cataracts results in high cost to society in terms of hospital days, dollars, and individual discomfort. Society would benefit from the prevention of cataracts. On the other hand, cataracts are readily amenable to treatment by surgery with relatively little risk. Other conditions that may not be as prevalent or as costly to society are not as readily ameliorated and hence are a greater challenge and in a sense represent a greater problem.

The ultimate prevention of cataracts and other visual disorders depends upon a more complete understanding of basic processes—normal structure, growth, development, and health maintenance—as well as factors that alter these processes such as aging, trauma, infections, nutrition, environment, drugs, genetics, and neoplasms. The state of knowledge at this time suggests that long-term advances depend on vision research and training which are built on the fundamental disciplines such as biochemistry, physiology, pathology, immunology, microbiology, and anatomy. The importance of basic research of this type to clinical advances and new forms of treatment has been well documented.[6]

3

Recommendations

THE RESEARCH TRAINING programs now administered by the National Eye Institute have had a profound effect on the Nation's capacity to conduct research on vision and its disorders. The number of qualified individuals and organized units actively engaged in vision research has been greatly increased through the programs NIH has supported during the last two decades.

DHEW biomedical research training programs were reevaluated by the Office of Management and Budget a short time ago, and in 1975 the Congress enacted new training legislation which necessitated the issuance of new guidelines by NIH. Graduate Training Grants (T01), which were instrumental in the organization of research groups and departments of ophthalmology, and Special Research Fellowships (F03), which supported advanced clinical and clinical research training, were discontinued as a result of the new legislation. The National Eye Institute's own training guidelines placed greater emphasis on the development of individuals who would have lifelong careers in vision research.

It is still too early to evaluate the full effects of the new course that was set. In considering possible recommendations for the future of the National Eye Institute vision research training support, the *Vision Research Training* Panel believes nine are worthy of mention. The first four are in line with current practice and are listed as a reminder of their importance. The last five call for adjustments in existing training policy to meet perceived needs.

Need for Excellence

The National Academy of Sciences has been given the continuing responsibility for studying the personnel needs of biomedical and behaviorial research, and its recommendations will serve as guidelines for the implementation of the National Research Act of 1974. The training policies of the National Eye Institute have been in accord with and, in fact, have anticipated the recommendations of the Academy. The Academy, like the National Eye Institute, emphasizes the need to sustain the quality of the research environment to improve the chances that efforts will be directed toward research leads that will result in major advances against disease and disability.

Need for Stable, Consistent Policy

As a result of the training programs of the National Eye Institute, departments and sections of ophthalmology, schools and colleges of optometry, and other

centers throughout the United States have developed or strengthened their research components so that multidiscipline groups with active programs now exist. These groups are generally small, and the stability of their newly acquired capacity for research depends on the continuity of funds for vision research and training. A consistent policy for vision research training which is systematically regulated is essential to maintaining the gains that have been made. The National Academy of Sciences supports this concept, and it is reflected in the National Eye Institute's orderly introduction of the National Research Service Awards and phasing out of the types of awards that they supersede.

Need for Vision Research and Training in the Basic Sciences

At the present time, most of the Institutional National Research Service Awards are made to departments or groups involved in basic research. This is largely because the terms prescribed for predoctoral and postdoctoral fellowships coincide with practices and stipends in basic science departments. Vision research benefits from the interest that is generated in these departments. First, the number of investigators that are active in vision research is increased if individual faculty members choose to conduct research in their disciplines on problems related to vision. Second, the discipline-oriented environment may suggest concepts and approaches that are less likely in a clinical setting. Third, predoctoral programs of graduate schools are conducted in basic departments—the place and time at which the research interests of future faculty members are frequently determined.

Need for Training in a Clinical Setting

Institutional National Research Service Awards that are administered by a clinical department with a complement of established investigators are most useful in providing particular types of training. For individuals with Ph.D. degrees who are interested in vision research, the clinical setting offers an excellent base in which to become acquainted with a broad multidiscipline field. For individuals with professional clinical training who are interested in academic careers, postdoctoral fellowships offer a means of learning the methods and approaches of biomedical research. For individuals at a predoctoral level who have an interest in medical research, a clinical department with faculty members who hold joint appointments in a graduate school offers an exciting setting in which to meet their research requirements.

Need for Individual Fellowships

Recipients of Individual National Research Service Awards are selected by national competition. An increasing percentage of new Ph.D. graduates are seeking postdoctoral fellowships as a means of obtaining an independent research experience. The field of vision research benefits by having this award; however, the operation of the program is hampered by delays in deciding who will be supported and whether funding will be available. This limits the pool of potential applicants and favors the more expeditious management of fellowships that is possible in departments with institutional awards. This, in turn, limits the pool of

potential preceptors. Therefore, it is recommended that the processing of applications for Individual National Research Service Awards be modified to expedite the commitment of awards. The Panel suggests that reviews be made several times each year and that a system of advanced funding be established so that monies are assured for all approved applications scheduled to be funded.

Need for Clinical Investigators

The greatest need for new research personnel is in clinical research. Clinicians are continually challenged and stimulated by the problems they observe in patients.

If, in addition to being clinicians, individuals are also trained investigators, the likelihood of having research directed toward the solution of clinical problems is increased. If several individuals, each of whom is expert in a different discipline, are working together in the same department or unit, the chances of productive results are still greater. Doctoral programs in the professional schools are generally directed toward producing clinicians rather than research scientists. Therefore, it is important to support postdoctoral training of clinicians who are willing to spend at least one year, and preferably two, in a basic science department or a well-staffed clinical department where the advancing frontiers of a discipline are explored and where a problem related to vision can be investigated in association with scientists working on analogous problems in other fields.

National Research Service Awards, for individuals who have just received a doctoral degree, and Academic Investigator Awards, for individuals who have completed the formal requirements of a residency, are the training mechanisms of choice for supporting this type of training experience.

Current NEI guidelines limit the number of Academic Investigator Awards to six per year with not more than one being given to a single institution. Institutions are requested to assure a faculty position for the recipient. These limitations and the seeming lack of general awareness of the availability of the Academic Investigator Award are a major deficiency in the NEI's mechanisms for facilitating the career development of young scientists. The Panel recommends that the number of Academic Investigator Awards be increased, that the limitation on the number of awards per institution be removed, and that assurances of faculty status be limited to the period of funding. Successful awardees should look forward to future support through Research Career Development Awards or regular research project grants.

It is recognized that ophthalmology residency training prepares an individual for a career in general ophthalmologic practice. There is a great need for clinical investigation in this field and therefore for advanced clinical research training in specific areas where clinical problems can be delineated and where attention can be paid to the development and evaluation of new methods of diagnosis and treatment. Existing training programs do not adequately accommodate the full range of clinically oriented candidates. The Clinical Investigator Award (K08) or a modified Academic Investigator Award (K07) could be adapted to meet this need. Such clinical research training would have to be directed by an expert in the specialized clinical field, and the application for the award would have to outline a specific program of training in clinical investigation. Applicants would be chosen from among those who have shown excellence in clinical ophthalmology and optometry and who have demonstrated an interest in pursuing an academic

career. The Panel recommends that a detailed proposal for training clinical investigators be prepared by the NEI staff and submitted for consideration to the National Advisory Eye Council.

Need for Initial Research Support for New Investigators

The National Eye Institute offers Special Visual Sciences Research Awards (R23) to attract and support young investigators. Grants are limited to $10,000; however, there are no separate funds for this program, and applications are reviewed by the NIH Division of Research Grants Study Sections in competition with those from established investigators. Therefore, at present, there are few applications for this special award, and the concept of assisting young investigators with modest start-up grants is not being served.

The Panel recommends adding to the award base of $10,000 a professional salary component not to exceed $15,000. The Panel also believes that it is very important for the NEI to inform the NIH Study Sections and potential applicants of the purpose of Special Visual Sciences Research Awards. Finally, R23 applications should not compete directly with regular project grants (R01) in NEI funding decisions.

Need to Consider Program Emphasis

Support for research and training which are related to the prevention of disease warrants greater emphasis. This requires a basic understanding of normal biological as well as pathological processes and suggests a need for the training and support of basic scientists who are interested in and qualified to work in vision research. The Panel recommends that high priority be given to research and training programs that will lead to the prevention of visual disorders.

Need for a New Administrative Arrangement

As an instrument of public policy, the National Institutes of Health has been most successful in stimulating investigations in desired research areas by providing appropriate incentives. Until recently, research and training priorities in vision research seemed to correlate better with the demonstrated research interests of investigators rather than with priorities that are defined as public policy.

A case can be made for allowing the direction of research to follow the scientific interests of the investigator on the premise that a well-qualified and highly capable individual is best fitted to determine his or her potentially productive areas of research. On the other hand, the establishment of the National Eye Institute represents an action taken by the public to increase the endeavors of scientists in vision research. Clearly, broad national research policy must be established by blending the perceived interests of the public with the scientific knowledge of the investigator. This is accomplished in part through a group with broad representation such as the National Advisory Eye Council.

Vision research training should be directed toward providing the personnel required to meet the stated objectives of vision research. In vision research training, the opportunity of using resources as an instrument for implementing policy is hindered by the fact that funds for training and career development programs as established by Congress for each fiscal year are not freely interchangeable with funds designated by Congress for research program budget categories. In addition, more than one group is involved in reviewing applications for training support. The Panel recognizes that needs for research training will vary with scientific advances and the availability of funds. For instance, in areas or times when expanded activity is desired a greater emphasis might be placed on programs that produce new investigators. Whereas, in areas or times of stable support emphasis should be directed toward programs for more established individuals so that research productivity will be increased.

The Panel believes, therefore, that optimal results can be obtained if all resources for training in vision are in effect pooled; a quantitative five-year program plan that is updated each year projects the allocation of funds among different types of training programs and among the five major fields of research that are supported by the National Eye Institute; and pending the adoption of a more unified approach to training, the staff of the National Eye Institute is encouraged to modify training guidelines and seek applications in accord with established research priorities.

4

Training Needs for 1978-1980

IN THE PROJECT and Resource Tables that accompany the preceding reports of the program planning Panels, estimates are provided of the number of new principal investigators that will be required during the period 1978-1980 to carry out the recommendations in each of the five major areas of vision research supported by the National Eye Institute. It is important to emphasize that in making these estimates, the Panels took into consideration not only the need for newly trained investigators, but the likelihood that established scientists presently working in other fields of research could be attracted to working on related problems in vision. Furthermore, the Panels took into account the fact that there are many experienced younger investigators who would be capable of assuming principal investigator positions during this period.

It was one of the responsibilities of the *Vision Research Training* Panel to determine how many of these additional principal investigators will have to be newly trained and consequently to present estimates of future budget requirements for vision research training and career development awards. The *Vision Research Training* Panel's recommendations are based on four premises:

1. There will be a continuing need to support the development of vision research personnel inasmuch as (a) there are, as documented in this report, a wealth of opportunities in vision research that promise major advances against the leading causes of blindness and visual impairment, (b) new research techniques and instruments continue to be developed which create a demand for new knowledge and skill, and (c) research in vision is enhanced if individuals initially qualifying in basic science or in a clinical field obtain additional experience in the other environment.
2. Ninety-six percent of vision research in the United States is federally funded. Of this amount, the National Eye Institute supports 73 percent. Research training support by the NEI should be commensurate with its overall support of the field of vision research.
3. In the past few years, a cadre of competent investigators has been trained to meet many of the demands of vision research; therefore, it is possible to decrease somewhat the rate of growth for training support in the 1978-1980 period and in subsequent years.
4. There is a certain amount of mobility of scientists among related fields of interest. Vision research should continue to benefit from this mobility. Therefore, it is not necessary to budget for training the total number of required individuals.

Based on an assessment of existing manpower in the various areas of vision research, the realistic likelihood that a certain number of investigators from other fields will enter vision research, and the expected availability of funds, the Panel proposes that the Council budget for 1978 provide for an additional 23 career type training awardees and an additional 115 fellows and trainees for programs that last an average two to three years. Thus, provision is made for training only about 23 percent of the total need for new principal investigators during the period 1978-1980.

Training needs vary with the specific plans in individual programs. *Retinal and Choroidal Diseases*, for example, which represents 48 percent of the projected FY 1978 research funds (research grants, contracts, and centers), is judged to require only about 36 percent of the training and career development funds because a large proportion of the research dollars in this program are designated for multi-center clinical trials. Such trials draw in great part upon existing staff of academic institutions, many of whom are not otherwise directly involved in research.

The following is the *Vision Research Training* Panel's recommendations for the numbers of newly trained investigators who will be needed during the period 1978-1980 to help fulfill the total manpower requirement projections made by each of the disease program Panels.

	New Principal Investigators Required for 1978-1980	Need for Newly Trained Investigators 1978-1980
Retinal and Choroidal Diseases	208	49
Corneal Diseases	100	21
Cataract	46	8
Glaucoma	54	14
Sensory and Motor Disorders of Vision	192	46
TOTAL	600	138

5

Summary

THE NATIONAL EYE INSTITUTE has supported training programs that have resulted in the development of individuals and centers that are capable of responding to research needs in vision and its disorders. Current programs are summarized in Table 11. The program is reviewed periodically, and in this report suggestions are made for meeting needs as they are perceived at this time.

Table 11

National Eye Institute Mechanisms for Support of Research Training and Career Development[1]

NEI Mechanism	Stipend	Eligibility	Commitment	Areas of Research Training
		Research Training*		
Predoctoral				
National Research Service Award (T32) (Institutional Research Training Program)	$3,900	Predoctoral level; Citizen or noncitizen national or permanent visa	2-3 years; Payback provision	Immunology; Genetics; Pharmacology; Epidemiology; Physiology; Biochemistry; Developmental Biology; Psychophysics and Physiological Optics; Pathology
Postdoctoral				
National Research Service Award (F32) (Individual Postdoctoral Fellowship)	$10,000 to $14,000; $3,000 to institution	Postdoctoral level; Citizen or noncitizen national or permanent visa	2-3 years; Payback provision	Retinal and Choroidal Diseases; Corneal Diseases; Cataract; Glaucoma; Sensory and Motor Disorders of Vision
National Research Service Award (T32) (Institutional Research Training Program)	$10,000 to $14,000	Postdoctoral level; Citizen or noncitizen national or permanent visa	2-3 years; Payback provision	Immunology; Genetics; Pharmacology; Epidemiology; Physiology; Biochemistry; Developmental Biology; Psychophysics and Physiological Optics; Pathology
		Career Development**		
Academic Investigator Award (K07)	Up to $25,000 plus fringe benefits; $5,000 for equipment, supplies and travel	Citizen or noncitizen national or permanent visa; 3-7 years post-doctoral level or post-residency (Exceptions to post-doctoral level may be made for change of field)	3 years	Epidemiology; Clinical Trials
Research Career Development Award (K04)	Up to $30,000 plus fringe benefits and indirect costs	Citizen or noncitizen national or permanent visa; Principal Investigator on research grant with 3 years support remaining	5 years	Retinal and Choroidal Diseases; Corneal Diseases; Cataract; Glaucoma; Sensory and Motor Disorders of Vision

*Laboratory and clinical research training in sciences relating to diseases and disorders of the visual system

**Guided laboratory and clinical research experience relating to diseases and disorders of the visual system

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Appendix: Pertinent Sections of

*Personnel Needs and Training for Biomedical and Behavioral Research**

FEDERAL ROLE AND TRAINING QUALITY

ONE OF THE original intents of federal support of research training was to augment the supply of researchers to meet the then-growing demand. Based on the Committee's analysis of current and anticipated market demand, it believes that current personnel needs generally have been met in many biomedical and behavioral fields, although particular areas of shortage exist and will continue to arise. It should be remembered, however, that an increase in the number of researchers was only one goal of federal training support. Another was to bolster the quality of training programs and to ensure that training was available in areas of national interest.

The fundamental assumption linking the federal responsibility for research to a responsibility for training has been, and remains, that the quality of research depends primarily on the talents and training of the individuals attracted to a research career. The infusion of federal support has had not only a salutary impact on the needed supply of researchers, but has also led to a continued improvement in the overall standards of research training. Federal training grant/fellowship programs are now recognized as highly selective and conducive to quality training. In adjusting public policy to reflect changing market conditions, federal policy should seek to sustain and enhance this tradition of high-quality training.

The competitive process for awarding fellowship and training grant appointments assures the selection of the most talented and qualified applicants. This selection process acts as a quality-control device to set a high standard of excellence. In the fellowship program, students are selected individually through national competition; in the training grant program, quality is maintained by the peer review process of competing programs. Each of these support mechanisms is discussed in further detail in the following paragraphs and in Chapter 2.

The fellowship program follows a long tradition in this country of awards based upon individual ability and initiative as shown by past academic performance and personal characteristics. The training grant, through its institutional support, is designed to provide stability and to permit flexibility and innovation in research training—three factors that encourage continuity of excellence in an academic field.

Both fellowships and training grants make available a high degree of flexibility in choosing programs. The fellow may personally seek admission to different programs and departments at various institutions. The trainee is afforded great flexibility in choosing a course of study within his program because he is not bound to a specific project.

*The 1976 Report of the Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel, Commission on Human Resources, National Research Council, National Academy of Sciences, Washington, DC.

Training grants represent up to a 5-year commitment to support a broad range of training-related activities designed to establish and maintain an environment conducive to research excellence. As an independent source of funds that goes beyond the existing financial constraints of institutions and departments, training grants provide incentives for program innovation through start-up and ongoing support that can initiate inter- and multidisciplinary programs, overcome the inertia of the current academic disciplinary structure, and provide legitimacy for new discipline- or problem-oriented approaches. Thus, while fellowships and traineeships encourage talented students to pursue careers in research, training grants additionally enhance the ability of departments to prepare them for truly productive careers.

It should be noted as well that the training grant program has enabled many departments to be strengthened that otherwise might not have been. Institutions that may not have had uniformly strong programs have been able to develop strength and excellence within individual departments. In so doing, they often have strengthened related departments that have benefited from the training program and its ability to draw in related disciplines.

The peer review process, conducted through the funding agencies, tends to winnow out the less strong programs during competition for renewal. As the number of training grant awards has been curtailed in recent years due to budget constraints, the quality of remaining programs has constantly been heightened through the peer review system.

The Committee believes that the federal responsibility for health research training goes beyond the simple assurance of access to graduate and postdoctoral training, and extends to the provision of programs that are of a high level of excellence in areas relevant to the national interest. Such responsibility may include not only particular research problems but also the development of whole new areas of research need. Innovation in programs must continually be encouraged. Financial constraints placed on departments and institutions militate against their taking the initiative or being able to follow through on new ideas. The federal government's support is critical to such innovation and must therefore include, as much as possible, provision for program support as well as trainee support.

The following recommendations were noted by the Committee:

RECOMMENDATION 1: BASIC BIOMEDICAL SCIENCES

Currently available information on the projected employment market for research personnel in the biomedical sciences indicates the advisability of a modest but significant reduction of about 10 percent in the number of federally funded predoctoral candidates in that field from the level that existed in FY 1975. This reduction should be undertaken in FY 1976. Although this reduced level is shown in Table 1.1 and Figure 1.1 as being maintained through FY 1978, the Committee, during the coming year, will be studying in greater the effects of the recommended decrease in funding in order to determine whether an increase, a further decrease, or maintenance at that level is warranted. The Committee's Panel on Basic Biomedical Sciences intends to devise a feedback mechanism to assist in this monitoring effort.

The Committee also recommends that the number of federally funded post doctorals in FY 1975 in the basic biomedical sciences should be continued at this time without change. It is at this level of study that the most able investigators in the basic biomedical sciences receive their specialized training.

For predoctoral candidates, the Committee concludes that funding by the training grant mechanism represents the most appropriate form of federal research training support. In contrast, for postdoctoral students, the recommendation is that the majority should be funded through the fellowship program. This mechanism not only assures that high-quality candidates are selected through the national peer review process, but that rapid adjustments can be made in response to research opportunities in various areas. In addition, the fellowship mechanism makes it possible for high-quality individual training to be obtained in the selected field at the institution of the fellow's choice.

* * * * *

RECOMMENDATION 3: CLINICAL SCIENCES

The Committee concludes that the continued need for research-trained clinicians to investigate the

applicability of new biomedical knowledge to disease problems in man justifies some emphasis on post-M.D. research training in the immediate future. Although virtually all of the researchers in the clinical sciences are M.D.'s, similar principles for training needs also apply to the smaller group of other professional doctorate holders, such as dentists and veterinarians, and Ph.D.'s working in the clinical sciences.

The Committee recommends that 2,800 trainees and fellows at the postdoctoral level be funded by the end of FY 1977, and that this level be maintained during FY 1978. The Committee will continue to monitor this recommendation to determine future directions as further information is developed. This recommended level for FY 1977 represents a one-third decrease from the peak level of postdoctorals funded in FY 1969 (about 4,200), when clinical specialty traineeships and some clinical residencies were also being funded, but a 10 percent increase over the number funded by the NIH in FY 1975 (about 2,550).

The physician, although trained for clinical practice, has usually not had the same formal training in scientific research as a person who has earned the Ph.D. degree. There is a need for high-quality programs specifically designed to provide the rigorous scientific background necessary to produce a clinician with the skills necessary to be a productive research scientist. The Committee therefore concludes that most of the federal funding in this field should be in the form of training grants. A ratio of about 80 percent in traineeships and 20 percent in fellowships is considered appropriate.

The Committee took special note of the NIH-sponsored Medical Scientist Training Program, which supports graduate level training in medically relevant scientific fields, leading usually to the award of both the M.D. and Ph.D. degrees. It recommends that approximately 600 trainee positions be funded in FY 1977, an increase from the 581 positions authorized in FY 1976 and the approximately 550 trainees supported in FY 1975.

With regard to priority areas, the report notes:

BASIC BIOMEDICAL SCIENCES

The continuing availability of an adequate number of investigators from existing training programs, the broad base of the training they have received, and the close relationship among many basic biomedical disciplines have led to a substantial degree of mobility between different disciplines.

The implication of these findings with respect to designation of specialty areas for research training for predoctoral support is that important areas of research can be adequately staffed by personnel emerging under the existing types of training programs. This has led the Committee to conclude that designation of specialty areas is not warranted at this time. With regard to postdoctoral research training, the Committee will study this matter in the coming year to determine if specific areas can be identified for special consideration.

CLINICAL SCIENCES

The Committee recognizes that important clinical advances often depend upon research in biomedical or physical sciences not originally directed toward the diagnosis, treatment, or prevention of specific diseases. Nevertheless, full application of basic knowledge to the solution of clinical problems often requires that additional personnel be trained for research in particular clinical fields after they have received their professional degree. The Committee is aware of some areas of research training that have been suggested by leaders in this field as justifying special consideration, but has concluded that the data presently available are insufficient to permit a firm conclusion on this matter at this time. The Committee will review these and other suggestions for special consideration in subsequent reports. In the interim, as the basic guiding principle, it recommends that primary emphasis be given to training for research on the etiology and pathogenetic mechanisms of disease; it is in this way that the greatest progress will be made in the ultimate prevention and treatment of diseases.

SUMMARY

Findings from the preceding analyses of the Ph.D. labor markets in the biomedical and behavioral sciences differ from conclusions reached about the need for clinical and health services researchers. Most basic biomedical and behavioral research is performed by persons with academic

doctorates, and there is some evidence that the employment opportunities for these, as well as other Ph.D. scientists, will not abound as they did during the 1960's. The annual growth rates of both R and D expenditures in academic and total (graduate and undergraduate) enrollments—and primary determinants of demand for basic biomedical and behavioral Ph.D. recipients—have already declined, and the Office of Education projections show that enrollments should level off by 1980.

On the supply side, the number of Ph.D.'s awarded annually in the biomedical and behavioral fields, although not increasing as rapidly as in previous years, will substantially exceed the loss due to attrition, resulting in an expected annual net growth in these labor forces of 5.5 and 8.4 percent, respectively. As an immediate consequence of the potential supply/demand imbalance, the Committee anticipates that an increasing proportion of the Ph.D. recipients in these fields will not find employment that fully utilizes their research training. A slight decrease in the research activity of recent graduates has already been observed. Postdoctoral study in both these fields has become increasingly popular and may, in fact, postpone some of the impact of the deteriorating employment markets for those earning Ph.D.'s. Eventually the shortage of attractive employment opportunities may discourage some of the most capable students from pursuing doctoral training in the biomedical and behavioral sciences, especially if there are more promising career opportunities available in other areas.

Research in the clinical fields is generally performed in medical and other health professions schools by persons with professional doctorates who have had some research training. Although the precise size of this pool is not known, there is some evidence that it is shrinking. According to data from the American Medical Association, the number of physicians involved primarily in research-related activities has decreased significantly since 1968. NIH-supported research training at the postprofessional level also has been declining. On the demand side, medical school faculties have been expanding at more than 6 percent annually, with no indication of decelerating. While some of these additional faculty positions may be filled by persons with Ph.D.'s, the Committee is concerned by the apparent decline in the research involvement of professional doctorate-holders. As emphasized in Chapter 2, the M.D. researcher, with his knowledge of the diseases of man, plays an important role in extending the fundamental research of the basic scientist to the area of clinical medicine.

The rapidly growing need for health services research personnel, although not easily measured because of the small size of the field and its interdisciplinary nature, is reflected by the sharp rise in federal R and D expenditures in this area during the past several years. Other factors, including increases in graduate enrollments (in selected disciplines) and federal expenditures on health care delivery, also have contributed to the expansion in research activity in this area. However, little information is available on the number of persons qualified to work in health services research. These persons come from a variety of disciplines and may hold either a professional or academic doctorate. Despite the lack of more precise data, the Committee is convinced that continued support of graduate students through training programs is needed to provide an adequate number of qualified researchers in the health services area to meet the rapidly growing demand.

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